(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 February 2004 (19.02.2004)

PCT

(10) International Publication Number
WO 2004/014929 A1

(51) International Patent Classification[7]: C07H 15/18, 5/06, 23/00

(21) International Application Number: PCT/AU2003/001008

(22) International Filing Date: 8 August 2003 (08.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2002950657 8 August 2002 (08.08.2002) AU

(71) Applicant *(for all designated States except US)*: **AL-CHEMIA PTY LTD** [AU/AU]; 3 Hi-Tech Court, Brisbane Technology Park, EIGHT MILE PLAINS, Queensland 4113 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WEST, Michael, Leo** [AU/AU]; 364 Hemmant and Tingalpa Rd, HEMMANT, Queensland 4174 (AU). **ANDREWS, Peter** [AU/AU]; 311 Swann Road, ST LUCIA, Queensland 4067 (AU). **RAMSDALE, Tracie, Elizabeth** [AU/AU]; 160 Hellawell Road, SUNNYBANK HILLS, Queensland 4109 (AU). **MEUTERMANS, Wim** [BE/AU]; 293 Birdwood Terrace, TOOWONG, Queensland 4066 (AU). **THANH LE, Giang** [AU/AU]; 38 Tarrant Street, MT GRAVATT, Queensland 4122 (AU). **CLARK, Chris** [AU/AU]; 4/21 Waverly Road, TARINGA, Queensland 4068 (AU). **ABBENANTE, Giovani** [AU/AU]; 53 Pringles Road, SAMPSONVALE, Queensland 4520 (AU). **LIU, Ligong** [AU/AU]; 28 Samara Street, SUNNYBANK, Queensland 4109 (AU).

(74) Agent: **CULLEN & CO.**; Level 26, 239 George Street, BRISBANE, Queensland 4000 (AU).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

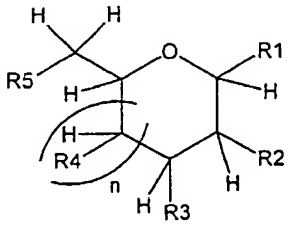
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/014929 A1

(54) Title: DERIVATIVES OF MONOSACCHARIDES FOR DRUG DISCOVERY



(I)

(57) Abstract: New compounds and methods for the preparation of combinatorial libraries of potentially biologically active compounds are based on monosaccharides of formula (I) being a derivative of a furanose or pyranose form of a monosaccharide.

DERIVATIVES OF MONOSACCHARIDES FOR DRUG DISCOVERY

FIELD OF THE INVENTION

This invention relates to new compounds and methods for the preparation of combinatorial libraries of potentially biologically active compounds based on natural and unnatural monosaccharides. These compounds are functionalized, with a view to varying lipid solubility, size, function and other properties, with the particular aim of discovering novel drug or drug-like compounds, or compounds with useful properties. The invention provides intermediates, processes and synthetic strategies for the solution or solid phase synthesis of monosaccharides, variously functionalised about the sugar ring, including the addition of aromaticity and charge, the addition of pharmacophoric groups and the placement of amino acid and peptide side chain units or isosteres thereof.

BACKGROUND OF THE INVENTION

In the field of drug discovery there is a constant need for novel scaffolds that enable the rational design of potentially bioactive molecules. Carbohydrates have recently come under scrutiny as offering a source of scaffolds that allow for a high degree of substitution, and offer access to both functional and structural diversity. The nature of monosaccharide molecules is such that there are numerous different stereoisomers available that can provide access to a greater degree of molecular space than do the scaffolds presently employed in drug discovery.

Carbohydrate monomers predominantly contain hydroxyl groups but also may contain other functionalities such as an amino and/or carboxylate function. In essence, the concepts involved in drug discovery through carbohydrate based molecular and structural diversity, are twofold: (1) The primary concept involves the exploitation of the high functional density found around the carbohydrate ring to display several different moieties of biological relevance. There is a dual significance to this substitution in that (i) the substituents relative position around the ring may be varied in relation to each other and, (ii) each individual moiety may be substituted for a class of such moieties and therefore themselves may be varied (by example: an arginine

mimetic may be substituted at position 1, 2, 3, 4 or 5 around a ring in relation to other peptidomimetics, by the same token the arginine mimetic may represent a class of different arginine bioisosteres which may all be similarly substituted). (2) The second concept involves exploiting the structural diversity inherent in carbohydrate isomers. Each of the substituents around a carbohydrate ring may theoretically be presented in either an axial or equatorial configuration allowing access to hugely diverse molecular space. Many monosaccharides are naturally occurring, which aside from being useful in their own right, present themselves as cheap starting materials to access more exotic configurations.

There are other factors that promote carbohydrates as useful building blocks for drug discovery, for example the relative positions of the functional groups on the sugar rings are conveniently spaced such that they can effectively enable mimicry of (for example), peptide motifs such as peptidic turns and loops, as well as cyclic peptides.

The major difficulty encountered in attempts to employ monosaccharides as scaffolds, is associated with monosaccharide chemistry. In the past carbohydrate chemistry was considered arduous, protracted and not cost effective. Particularly, the degree of orthogonal protection group chemistry required to allow free access to any one of a monosaccharide's functional groups (usually five) was deemed too high to ever be effected in a commercially viable manner. As a corollary, the more easily effected peptide synthesis only requires a maximum three orthogonal protecting groups, additionally the conditions required for peptide synthesis are often milder, thus peptide synthesis has so far been able to be effected more easily than carbohydrate synthesis. Fortunately, recent developments in synthetic carbohydrate chemistry have begun to allow regular access to carbohydrates as molecular scaffolds. In a recent patent application (PCT AU00/00025) we disclosed a range of orthogonally protected building blocks suitable for oligosaccharide synthesis. The building blocks presented in this application are also suitable for use as intermediates in the synthesis of compounds of the present invention, and represent compounds and methods which define the state of the art.

A large number of Carbohydrate based templates and scaffolds has now been published in the scientific literature. A review of the major contributions by Gruner et. al., (Chem. Rev., 2002, 102, p491-514) highlights this activity. Within the general literature, there are two distinct types of carbohydrate templates (i) sugar amino acids and (ii) carbohydrate scaffolds.

Sugar amino acids are carbohydrates which contain both an amine function and a carboxylic acid function, and are used in place of amino acids in peptide type syntheses. The synthesis of monosaccharides for this purpose is exemplified by the work of Fleet (Tetrahedron, 1996, 52, p10711; Tetrahedron Assym., 1996, 7, p387; Tetrahedron Assym., 1996, 7, p157) and Le Merrer (Tet. Lett., 1995, 36, p6887) for furanoid sugars, and by Dondoni (J.Org.Chem., 1994, 59, p6404), Vogel (J. Carbohyd. Chem., 1994, 13, p37) and Kessler (see chem rev. above) for pyranoid sugars.

Sugar amino acids have been used in peptide synthesis, and in the formation of linear oligomers for various biological purposes (see chem reviews above). Importantly, all of these compounds contain an amino function and a carboxylate function directly attached to the carbohydrate ring, and these functional groups are involved in amide bond forming processes which is the central concept in their use. The compounds of this type are distinctly different from the compounds of the present invention.

Carbohydrate scaffolds have also received considerable attention in the scientific literature, at least by way of desideratum. In concept, these compounds provide a chiral scaffold on which pharmaceutically active moieties are presented. This is the field of the present invention which adds to and is distinct from the state of the art.

The use of carbohydrates as scaffolds was promulgated by Hirschmann and co workers (Hirschmann et. al., J. Am. Chem. Soc., 114, 9217-9218, 1992) who employed this concept to develop a potent NK-1 receptor antagonist (Hirschmann et. al., J. Am. Chem. Soc., 115, 12550-12568, 1993), (Hirschmann et. al., J. Med. Chem., 39, 2441-2448, 1996). The fundamentals of this work have also been patented by Hirschmann et. al. (PCT/US1994/012233).

In a similar manner, Papageorgiou et al, have applied the concept to furanoid structures, developing weak somatostatin inhibitors in the process (Papageorgiou et. al., Bioorg. Med. Chem. Lett., 2, 135-140, 1992).

Weak inhibitors of integrin receptors and endothelin receptors have also been developed by applying this concept (Nicolaou, K.C., et. al, Tetrahedron, 1997, 53, p8751; Moitessier, N., et. al., Lett. Pep. Sci., 1998, 5, p75; Moitessier, N., et. al., Bioorg. Med. Chem., 2001, 9, p511.).

A number of other research groups have developed libraries of compounds based on this scaffold principle, and these groups are referred to in Gruner's review (vide supra). Despite the plethora of work to date, the compounds disclosed above have three common features which distinguish them from the current work: (i) all of the substituents are attached to the scaffold through an oxygen linkage, (ii) the anomeric position is always an O glycoside, and (iii) all of the available hydroxyl positions are substituted.

These features, when taken together, place significant limitations on the utility of the compounds. For example, ether linkages provide considerable rotational freedom and it is generally accepted that rotational freedom often results in diminished biological activity (Murphy et. al., J. Org. Chem., 68, 5692-5704, 2003). To this end, the present invention is directed to carbohydrate templates which have one or two amines directly attached to the carbohydrate ring, allowing the introduction of, for example, amide linked, sulfonamide linked, urea linked and carbamoyl linked moieties with significantly reduced rotational freedom and often better physical properties.

In a similar manner, the requisite for all of the positions to be substituted can lead to compounds of higher lipophillicity, higher molecular weight and lower solubility without imparting greater biological activity. In the present invention we disclose compounds with one or two hydroxyl positions unsubstituted, allowing generally improved solubility characteristics and lower molecular weights that would be expected for the corresponding fully substituted molecules.

These two features represent significant improvements over compounds described in the literature and are the result of considerable new method developments by the inventors.

Of all the carbohydrate scaffold work reported in the scientific and patent literature to date, we have found few examples of amine containing scaffolds outside the sugar amino acid class. Kunz et. al. (WO 99/07718) have claimed 2-deoxy 2-amino sugars as scaffolds for drug discovery. This citation does not teach or exemplify a compound with an amine group directly attached to the ring in the two position or any other position.

The disclosures in Kunz's relate specifically to the use of glucose, galactose and mannose as scaffolds and the methods described are not generally applicable to other monosaccharide scaffolds. In contrast, the compounds of the present invention are all O glycosides which are further limited by a narrow range of unsubstituted substituents dictated by the low reactivity of the sugar hydroxyls under the synthetic conditions disclosed. It is apparent that this technology displays significant disadvantages to the present invention; the efficiencies of conversion, the range of potential substituents, the various inversion chemistries that introduce both alternate oxy and amino stereochemical orientations, and the versatile alkylative chemistries of the present invention represent significant improvements over the methods of Kunz's application. Particularly, the present invention provides stereoisomers of monosaccharides that have a nitrogen or a carbon atom attached to the ring in positions 3,4,5 and 6 of a monosaccharide or tetrahydrofurano/pyrano ring system. Of particular interest to the medicinal chemist is the inclusion of linking functionalities that are likely to be stable to physiological conditions thus allowing the drug to reach the desired target intact, or in an active form.

Despite the general paucity of amine containing carbohydrate scaffolds in the literature, there are many examples of monosaccharide building blocks and protected aminosugars employed for oligosaccharide synthesis. By way of example, US 4818816 discloses a compound 1-methyl-2-carbobenzyloxy,3-benzyl glucosamine, a monosaccharide building block used in the synthesis of synthetic heparinoid oligomers. The compounds of the

present invention represent a significant departure from the simple building block type aminosugars, both in the diversity and complexity which is achievable. In order, to further distinguish the compounds of the present invention from the prior art, the use of standard amine protecting groups in carbohydrate synthesis is specifically excluded.

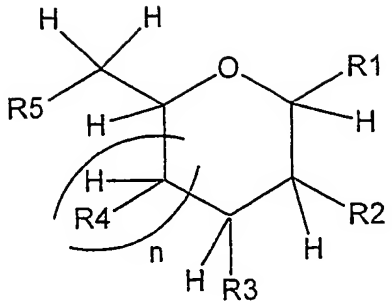
Sabesan (US patent 5,220,008) discloses a series of higher oligosaccharides as inhibitors on influenza. Within the claims of this patent, a partially protected monosaccharide (structure IV) is also disclosed. The compounds of this structure are protected monosaccharides for oligosaccharide synthesis which are known in the art and do not represent compounds for drug discovery.

Similarly, Alchemia Pty Ltd has disclosed in PCT/AU01/01307 building blocks, methods of syntheses, and final products relating to the employment of monosaccharide compounds as drug like molecules. The compounds of PCT/AU01/01307 are specifically directed at inhibitors of the muramyl cascade of enzymes and are hereby excluded from specification by the incorporation of this reference. A number of other publications relating to muramyl type compounds have appeared in the literature. Liu et. al. (Biorg. Med Chem Lett., 10, 2000, 1361-1363) present a series of compounds containing a benzyl glycoside at the anomeric position, an acetate at C-2 and a peptide homologated lactate at C-3 of a glucosamine scaffold. These compounds and those disclosed by Xiao (Peptides: Biol and Chem., Proc. 5th Int. Chinese Peptide Symp., 1998 CA: 134:178795) represent compounds and methods which help define the art of carbohydrate chemistry but are not directly relevant to the present invention.

It will be clearly understood that, if a prior art publication is referred to herein, this reference does not constitute an admission that the publication forms part of the common general knowledge in the art in Australia or in any other country.

OBJECT OF THE INVENTION

In a first aspect, the invention comprises a compound of formula I being a derivative of a furanose or pyranose form of a monosaccharide,



formula I

Wherein, n is 0 or 1;

R1 is XR wherein,

X is selected from O; S; S=O and SO_2,

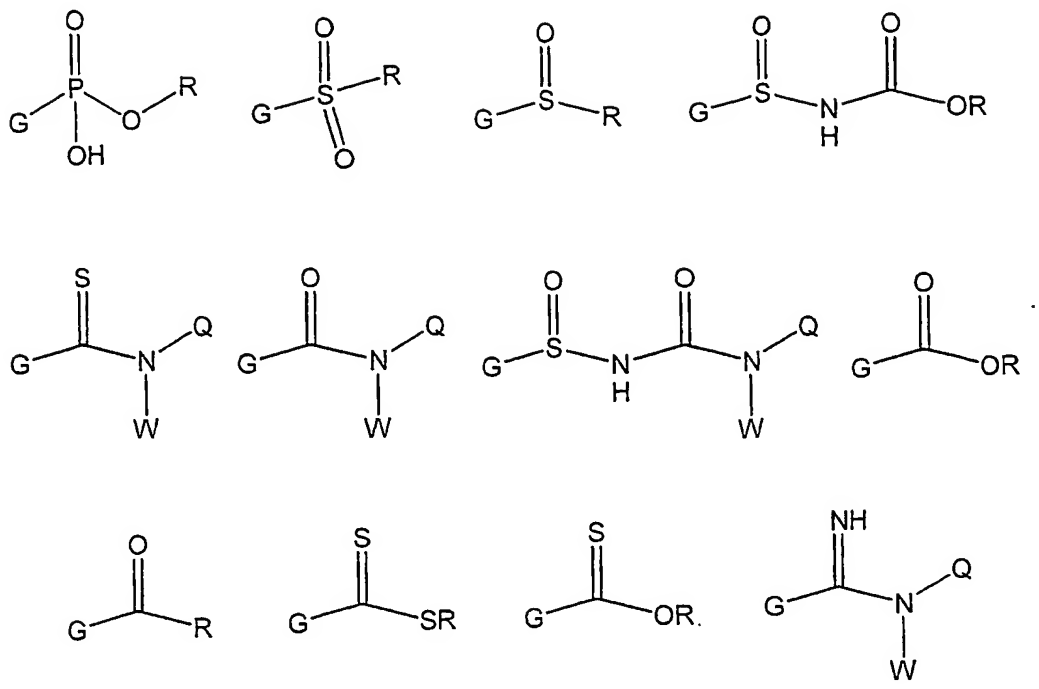
R is selected from the group consisting of C1 to C9 alkyl, C1 to C15 alkenyl, C1 to C15 alkynyl, C1 to C15 heteroalkyl, C6 to C15 aryl, C6 to C15 heteroaryl, C6 to C15 arylalkyl or C6 to C15 heteroarylalkyl which is optionally substituted, cyclic or acyclic, branched and/or linear,

The groups R2 to R5 are selected from OH, OR and N(Y)Z such that:

At least one of the groups R2 to R5 and not more than two of the groups R2 to R5 are OH,

At least one of the groups R2 to R5 and not more than two of the groups R2 to R5 are OR, where R is defined above, with the proviso that when two of the groups R2 to R5 are OR, the R groups may not both be methyl or unsubstituted benzyl,

At least one of the groups R2 to R5 and not more than two of the groups R2 to R5 are N(Y)Z, where Z is selected from hydrogen or R and Y is selected from the following, where G denotes the point of connection to the nitrogen atom in N(Y)Z, the N(Y)Z moieties may not be the same;



and the groups Q and W are independently selected from hydrogen or R as is defined above, and Q and W may combine to form a cycle,

The groups Z and Y may combine to form a cycle, and

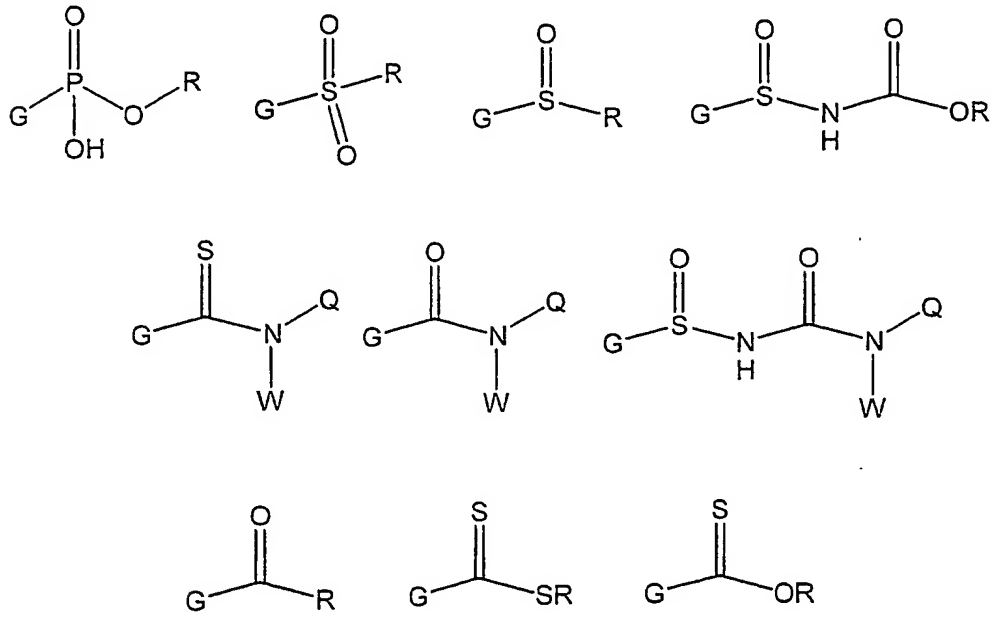
The groups R1 to R5 may not combine together to form a cycle.

In a more particular form the invention resides in a compound as described above with the proviso that where two groups in the compound of formula I are N(Y)Z, these groups are different, with the further proviso that when either R2 or R5 is N(Y)Z, N(Y)Z may not be azido, acetyl, benzyloxycarbonyl or t-butoxycarbonyl,with the further proviso that when R2 is N(Y)Z, N(Y)Z may not be phthalimido, 4-[*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]-amino}benzyl ester (ODmab), *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde), 2,2,2-Trichloroethoxycarbonyl (Troc), 9-Fluorenylmethoxycarbonyl (Fmoc), or a 5-Acyl-1,3-dimethylbarbiturate type protecting group (DTPM) and with the further proviso that when the scaffold is of the 2-deoxy-2-aminoglucose configuration and R5 and R4 are both hydroxyl, R3 may not be a glycolate [-CH_2-CO_2H] or lactate ether [-$CH(CH_3)$-CO_2H] or an ester or amide derivative thereof.

Suitably,the compound is a derivative of a furanose form of a monosaccharide, and wherein n is 0.

Suitably, the compound is a derivative of a furanose form of a monosaccharide, and wherein n is 0.

Suitably, the compound has n = 1,at least one of the groups R2 to R5 and not more than two of the groups R2 to R5 are N(Y)Z, where Z is selected from hydrogen or R and Y is selected from the following, where G denotes the point of connection to the nitrogen atom in N(Y)Z, the N(Y)Z moieties may not be the same;



And the groups Q and W are independently selected from hydrogen or R as is defined above, with the proviso that Y and Z may not both be hydrogen and where two groups in the compound of formula I are N(Y)Z, these groups are different, the groups Z and Y may combine to form a cycle, the groups R1 to R5 may not combine together to form a cycle, with the proviso that where two groups in the compound of formula I are N(Y)Z, these groups are different, with the further proviso that when either R2 or R5 is N(Y)Z, N(Y)Z may not be azido, acetyl, benzyloxycarbonyl or t-butoxycarbonyl,with the further proviso that when R2 is N(Y)Z, N(Y)Z may not be phthalimido, 4-[*N*-[1-(4,4-

dimethyl-2,6-dioxocyclo-hexylidene)-3-methylbutyl]-amino}benzyl ester (ODmab), *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde), 2,2,2-Trichloroethoxycarbonyl (Troc), 9-Fluorenylmethoxycarbonyl (Fmoc), or a 5-Acyl-1,3-dimethylbarbiturate type protecting group (DTPM) with the further proviso that when the scaffold is of the 2-deoxy-2-aminoglucose configuration and R5 and R4 are both hydroxyl, R3 may not be a glycolate [$-CH_2-CO_2H$] or lactate ether [$-CH(CH_3)-CO_2H$] or an ester or amide derivative thereof.

Suitably the heteroarylalkyl is substituted by a moiety from the group consisting of OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid, heteroaryloxy, aminoalkyl, aminoaryl; aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may be further substituted, with the proviso that the group R may not be or contain another saccharide moiety, a peptide, protein or amino acid.

The compound may be immobilized to a support. The support may be soluble or insoluble. Non-limiting examples of insoluble supports include derivatised polystyrene, tentagel, wang resin, MBHA resin, aminomethylpolystyrene, rink amide resin etc. Non-limiting examples of soluble supports include DOX-mpeg, polyethylene glycol etc.

DETAILED DESCRIPTION

Embodiments of the invention will be described with reference to the following examples. Where appropriate, the following abbreviations are used.

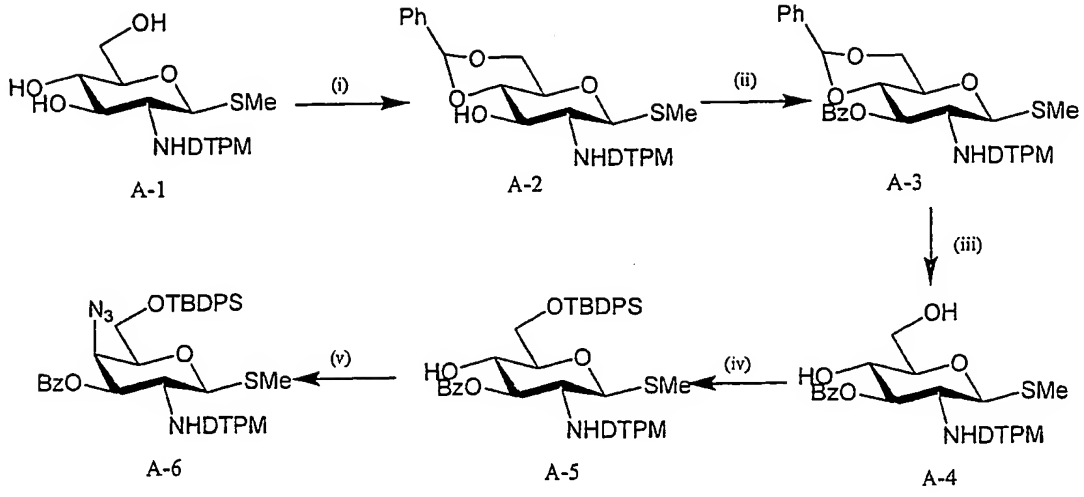
Ac	Acetyl
DTPM	5-Acyl-1,3-dimethylbarbiturate
Ph	Phenyl
TBDMS	t-Butyldimethylsilyl
TBDPS	t-Butyldiphenylsilyl

Bn	benzyl
Bz	benzoyl
Me	methyl
DCE	1,2-dichloroethane
DCM	dichloromethane, methylene chloride
Tf	trifluoromethanesulfonyl
Ts	4-methylphenylsulfonyl, p-toluenesulfonyl
DMF	N,N-dimethylformamide
DMAP	N,N-dimethylaminopyridine
□,□-DMT	□,□-dimethoxytoluene, benzaldehyde dimethyl acetal
DMSO	dimethylsulfoxide
DTT	dithiothreitol
DMTST	Dimethyl(methylthio)sulphoniumtrifluoro- methanesulphonate
TBAF	tetra-n-butylammonium fluoride

Part A: Preparation of building blocks:

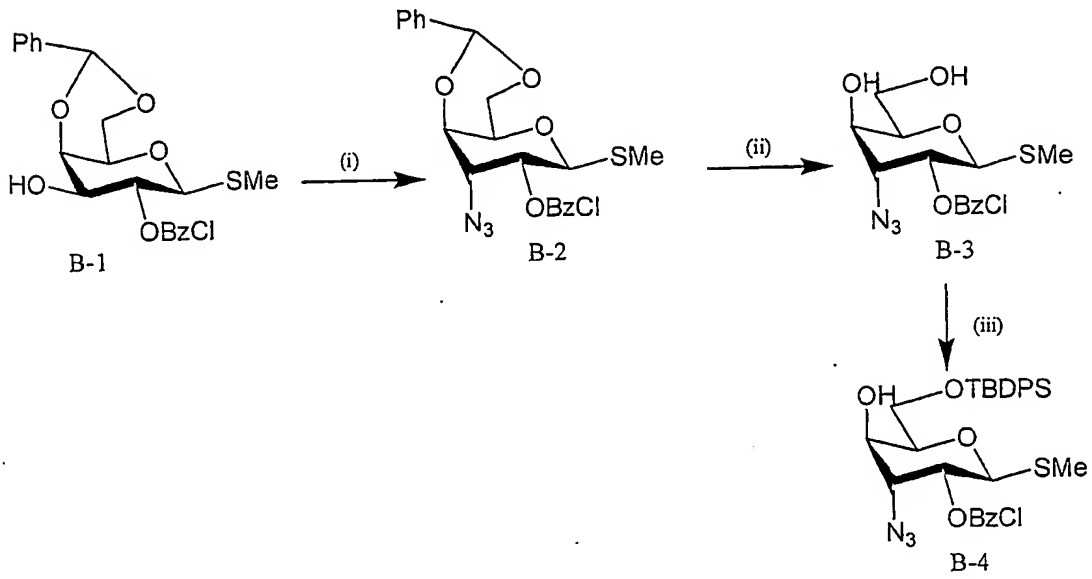
In order to fully enable the invention, we detail below methods for the preparation of certain building blocks used in the preparation of the compounds of the invention. The building blocks described are suitable for both solution and solid phase synthesis of the compounds of the invention.

Example A: Synthesis of a 2,4 dinitrogen containing Galactopyranoside Building Block



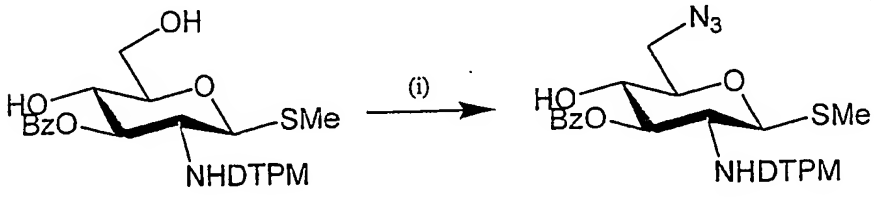
Conditions: (i) □,□-dimethoxytoluene (□,□-DMT), *p*-toluenesulphonic acid (TsOH), acetonitrile (MeCN), 76^{0}C, 85%; (ii) Benzoylchloride (BzCl), triethylamine; DCM, 99%; (iii) methanol (MeOH)/MeCN/water, TsOH, 75^{0}C, 98%; (iv) *t*-butyldiphenylsilylchloride (TBDPS-Cl), imidazole, pyridine, 120^{0}C, 99% ; (v) Tf_2O, pyridine, DCM, 0^{0}C, 100%;(b) NaN_3, DMF, 16hr, RT, 99%.

Example B: Synthesis of a 3-nitrogen containing Gulopyranoside Building Block



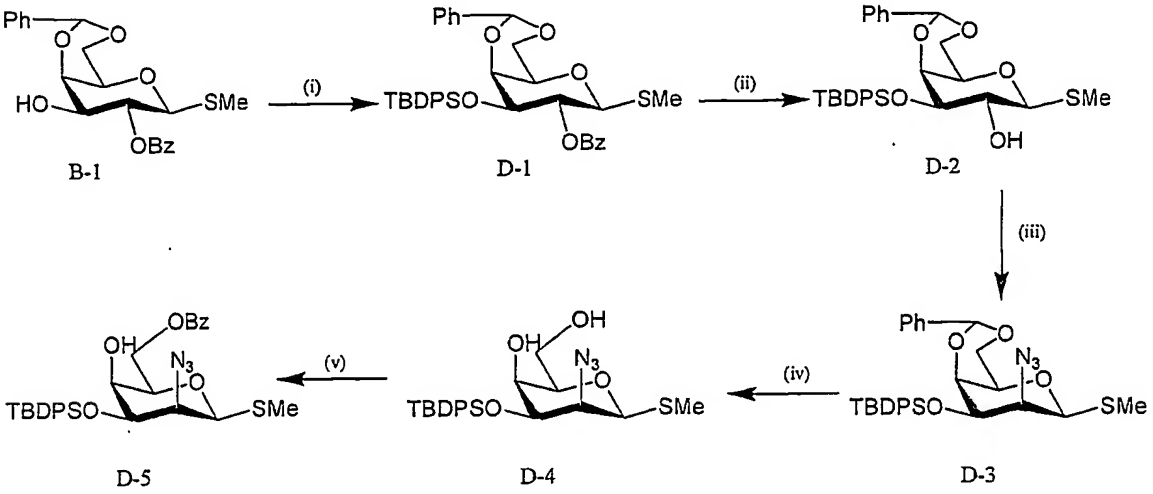
Conditions: (i) (a) trifluoromethanesulfonic anhydride (Tf_2O), pyridine, -20°C, dichloromethane (DCM), 1 hour, 100%, (b) sodium azide (NaN_3), *N,N*-dimethylformamide (DMF), 50°C, 5 hours, quantitative; (ii) TsOH, MeCN/ MeOH/water (12:3:1), 90°C, 6 hours, 88%(iii) TBDPSCl, DMAP, pyridine, 120°C, 12 hours, 93%

Example C: Synthesis of a 2,6-dinitrogen substituted Glucopyranoside Building Block



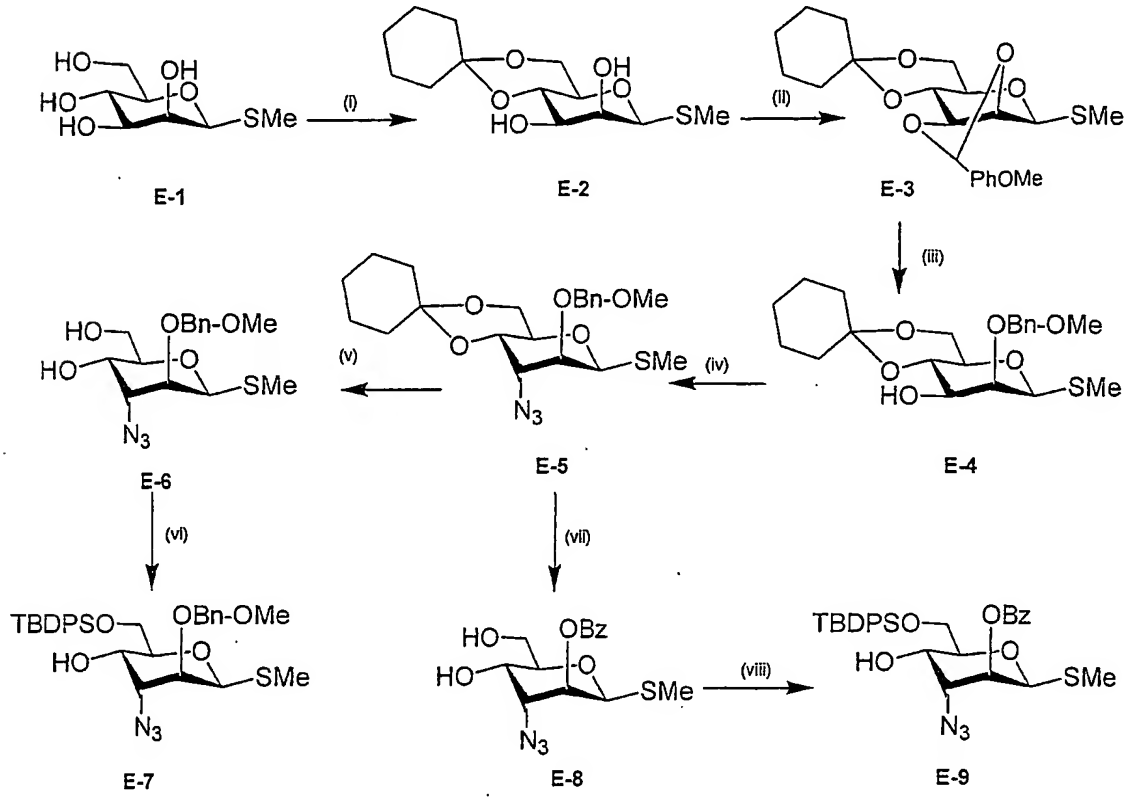
Conditions: (i) (a) Tosylchlodride, pyridine, RT, 24 hours, 33%(b) NaN_3, DMF, RT, 168 hours.

Example D: Synthesis of a 2-nitrogen containing Tallopyranoside Building Block



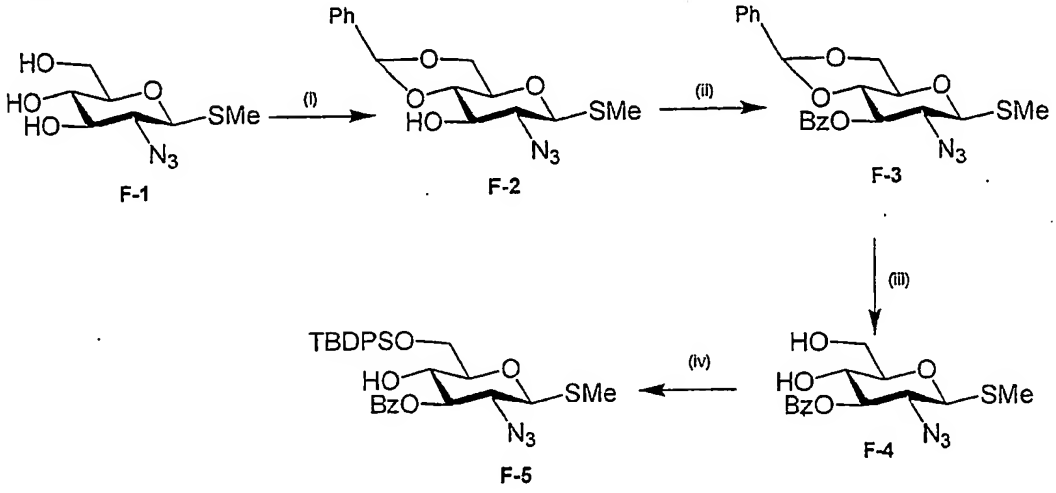
Conditions: (i) TBDPSCl, imidazole, 1,2-DCE, reflux; (ii) NaOMe/MeOH; (iii) (a) Tf_2O, pyridine, -20^{0}C, DCM, 1 hour, (b) NaN_3, DMF, 50^{0}C, 5 hours; (iv) TsOH, MeCN/MeOH/water; (v) benzoylchloride, DMAP, 1,2-DCE, -20^{0}C.

Example E: Synthesis of two 3-nitrogen containing Altropyranoside Building Block

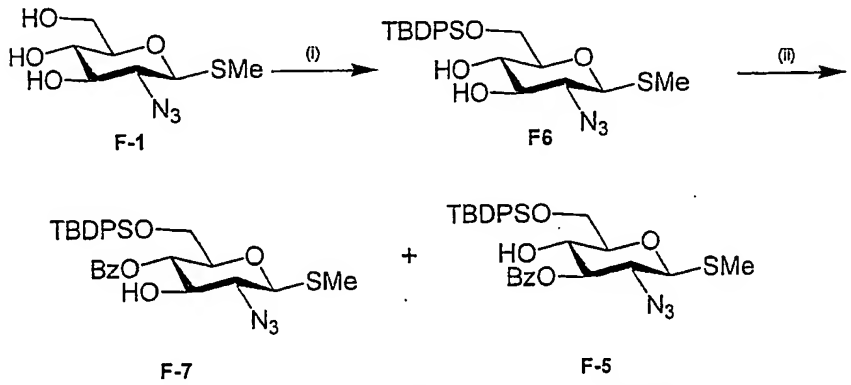


Conditions: (i) cyclohexanone dimethylacetal, TsOH, MeCN; (ii) *p*-methoxybenzaldehyde dimethylacetal, TsOH, MeCN; (iii) DIBAL, -78^{0}C, diethyl ether; (iv) (a) Tf_2O, pyridine, -20^{0}C, DCM, 1 hour, (b) NaN_3, DMF, 50^{0}C, 5 hours; (v) TsOH, MeCN/MeOH/water; (vi) TBDPSCl, DMAP, 1,2-DCE; (vii) (a) CAN, (b) BzCl, DMAP, 1,2-DCE, (c) TsOH, MeCN/MeOH/water; (viii) TBDPSCl, DMAP, 1,2-DCE.

Example F: Synthesis of a 2-nitrogen containing Glucopyranoside Building Block

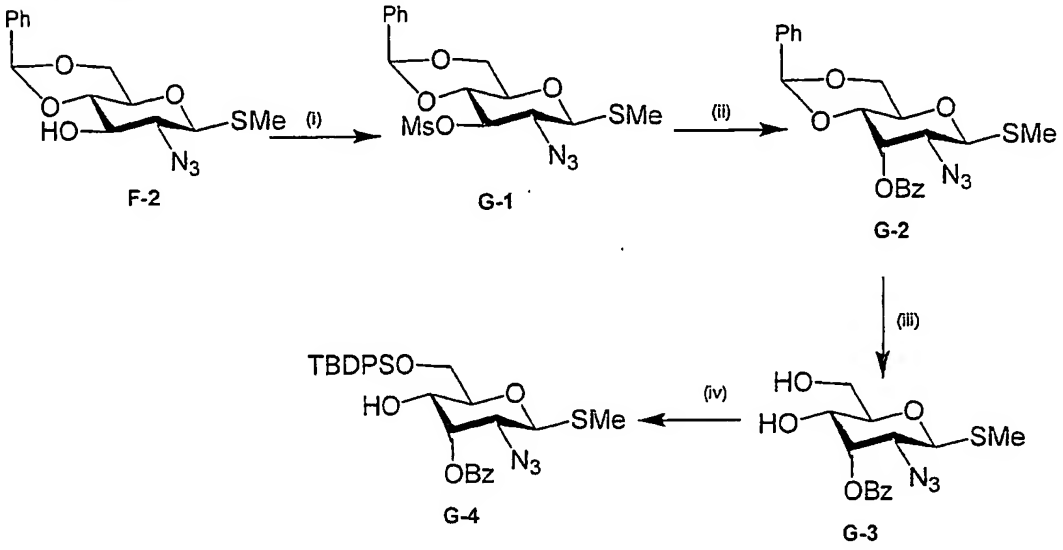


Conditions: (i) □,□-DMT, TsOH, MeCN; (ii) 1,2-DCE, BzCl, DMAP; (iii) TsOH, MeOH/MeCN; (iv) TBDPS-Cl, DMAP, 1,2-DCE.



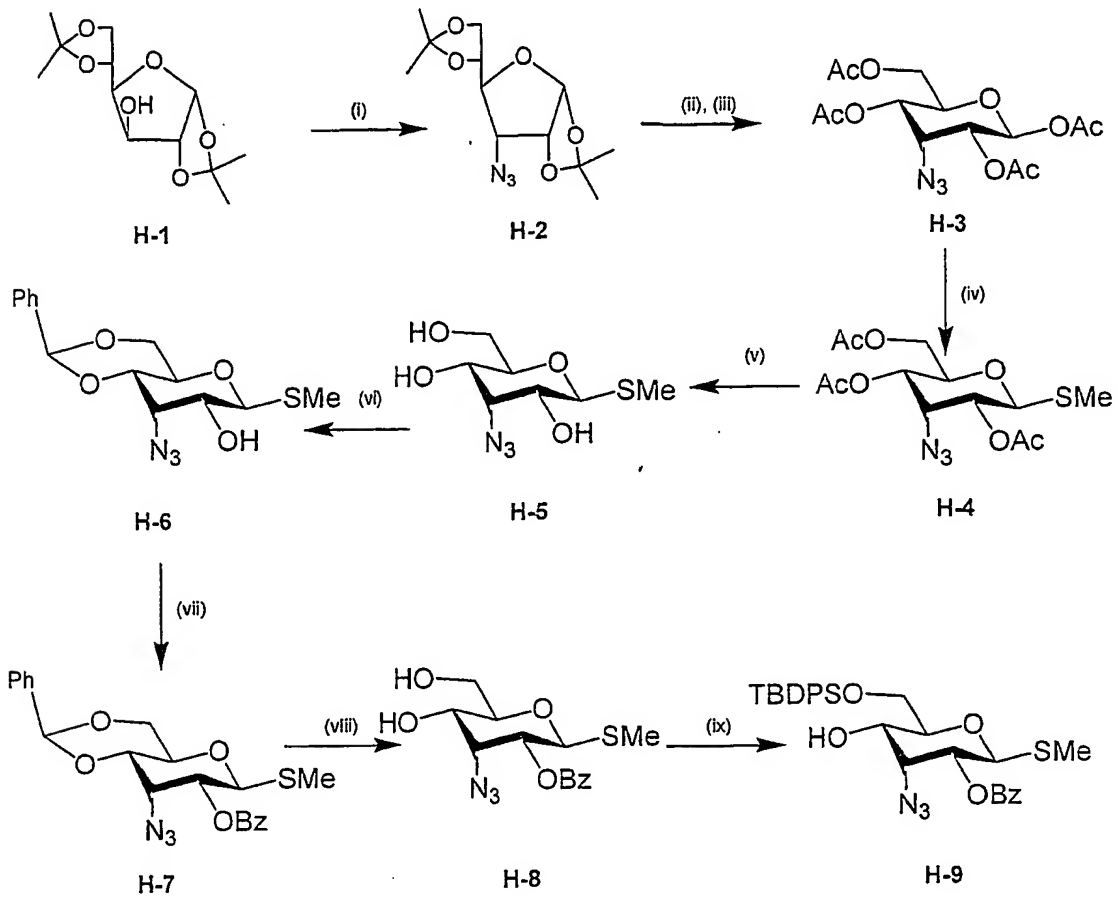
Conditions: (i) TBDPSCl, DMAP, pyridine, 120^{0}C, 0.5 hours, 81%; (ii) a. (Bu)2SnO, MeOH; b. Benzoylchloride, RT, 24 hour;

Example G: Synthesis of a 2-nitrogen containing Allopyranoside Building Block



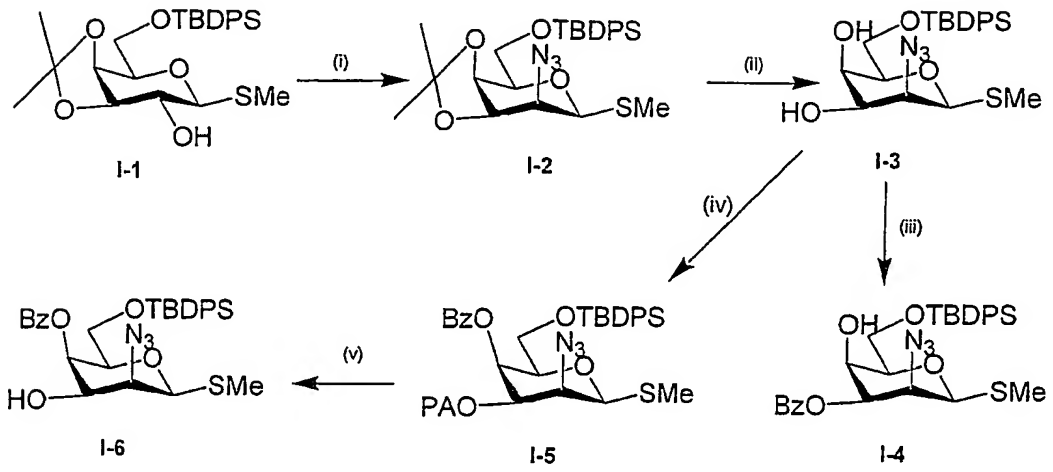
Conditions: (i) DCM/pyridine, MsCl, DMAP, O^0C; (ii) sodium benzoate, dimethylsulphoxide (DMSO), 140^0C; (iii) TsOH, MeOH/MeCN/water; (iv) TBDPS-Cl, imidazole, DCM, 1 hour, reflux.

Example H: Synthesis of a 3-nitrogen containing Allopyranoside Building Block



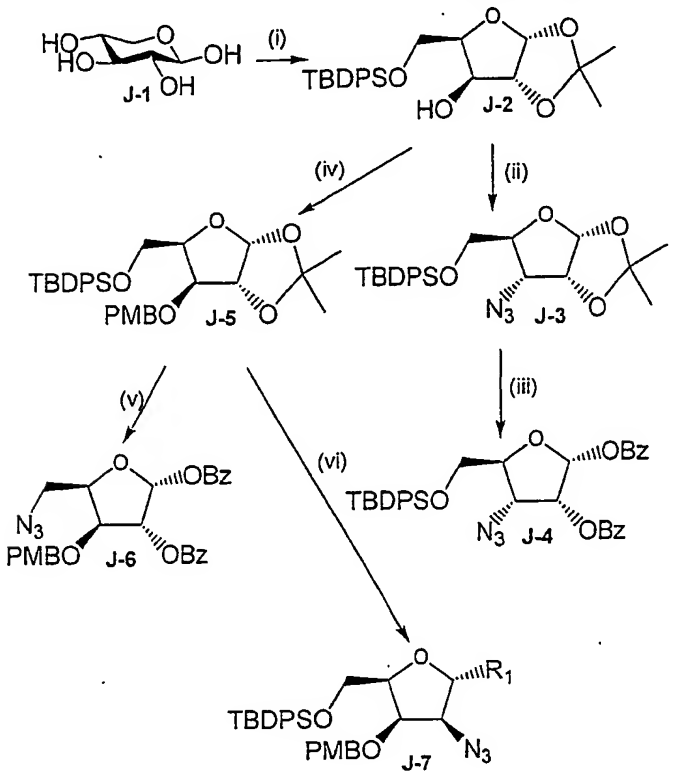
Conditions: (i) Tf_2O, pyridine, DCM; (b) NaN_3, DMF; (ii) acetone, H^+; (iii) Ac_2O, pyridine; (iv) hexamethyldisilazane, I_2, CH_3-S-S-CH_3; (v) NaOMe/MeOH; (vi) TsOH, □,□-dimethoxytoluene, MeCN; (vii) benzoylchloride, 1,2-DCE, pyridine, DMAP; (viii) TsOH, MeOH, H_2O, MeCN; (ix) TBDPS-Cl, imidazole, 1,2-DCE.

Example I: Syntheses of two 2-nitrogen containing Tallopyranoside Building Blocks with hydroxyls in the 3 or 4 positions.



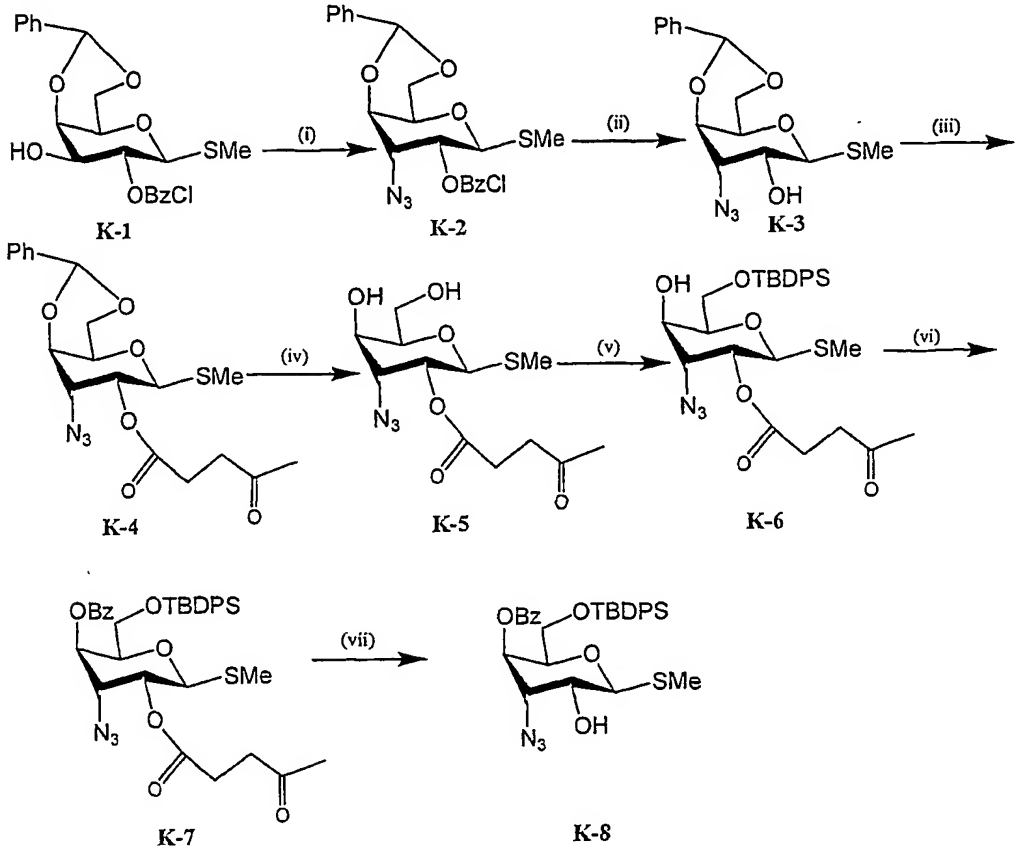
Conditions: (i) (a) Tf_2O/Py, (b) NaN_3, DMF; (ii) TsOH, MeOH/MeCN/water; (iii) BzCl, DMAP, 1,2-DCE; (iv) (a) phenoxyacetyl-Cl (PACl)/pyridine; (b) Bz_2O/pyridine; (v) $MeNH_2$/THF.

Example J: Synthesis of nitrogen containing furanoside Building Blocks



Conditions: (i) (a). 2,2-dimethoxypropane, TsOH, DMF; (b). TBDPSi-Cl, Imidazole, DMF; (ii) (a) Tf_2O/Py, (b) NaN_3, DMF; (iii) (a) TsOH, MeOH/MeCN/water; (b) Benzoyl chloride, pyridine, DCM; (iv) 4-methoxybenzyl chloride, NaH, DMF; (v) (a)TBAF, THF; (b) Tf_2O/Py, (c) NaN_3, DMF; (d) TsOH, MeOH/MeCN/water; (e) Benzoyl chloride, pyridine, DCM; (vi) (a) TsOH, MeOH/MeCN/water; (b) Benzoyl chloride, pyridine, DCM; (c) R-OH or R-SH, boron trifluoride diethyl etherate, DCM, molecular sieves; (d) Tf_2O/Py, (e) NaN_3, DMF;

Example K: Synthesis of a 3-nitrogen containing Gulopyranoside Building Block



K-1 K-2 K-3 K-4 K-5 K-6 K-7 K-8

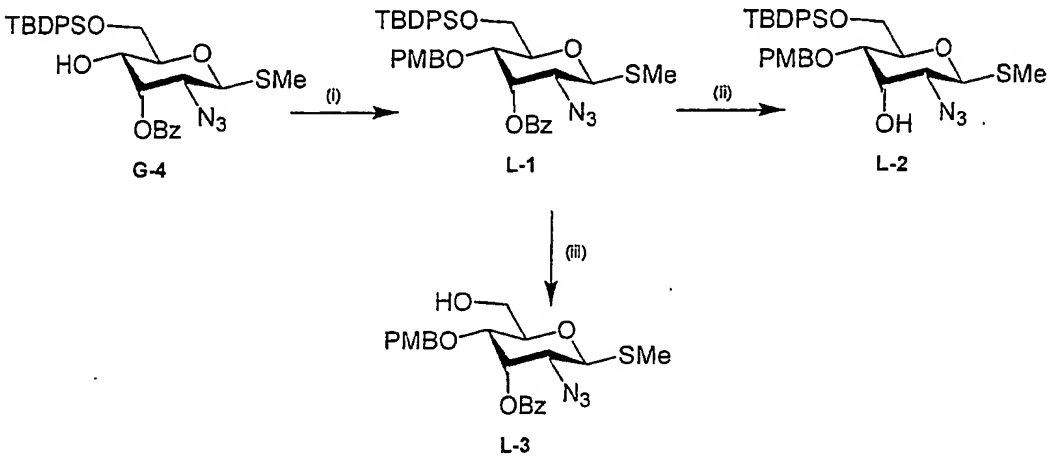
Conditions: (i) (a) trifluoromethanesulfonic anhydride (Tf_2O), pyridine, -20°C, dichloromethane (DCM), 1 hour, 100%, (b) sodium azide (NaN_3), *N,N*-dimethylformamide (DMF), 50°C, 5 hours, quantitative; (ii) NaOH/H2O/THF/MeOH, 99%; (iii) Levulinic acid, N,N'-dicyclohexyldiimide, DMAP, DCM, quantitative; (iv) TsOH, MeCN/ MeOH/water (15:15:1), 50°C, 16 hours, 56%; (v) TBDPSCl, DMAP, pyridine, 120°C, 2 hours, 85%; (vi) Benzoylchloride, pyridine, RT, 2 hour, 95%; (vii) hydrazine acetate, DCM.

Part B: Immobilization to solid support and glycosylation:

The compounds of the present invention may be conveniently prepared in solution phase or on a solid support. Because a free hydroxyl group is always present in the compounds of the invention, it is convenient to immobilize the

building blocks to the solid support through a hydroxy function which will become the free hydroxyl group in the final compounds. Many of the building blocks described above have a free hydroxyl in the 4 position which is suitable for immobilization. Where a free hydroxyl is desired in a different position, a protection/deprotection sequence is first performed.

Example L: Alternative immobilization positions



Conditions: (i) 4-methoxybenzyl chloride, NaH, DMF, workup with citric acid (ii) NaOMe/MeOH/THF; (iii) TBAF/THF; HOAc to neutral pH

Example M: Glycosylation of anomeric position

In most cases the thiomethyl glycoside building block containing one free hydroxyl group can be used in glycosylation reactions without resorting to protection of the free hydroxyl. An excess of the alcohol acceptor is typically employed. Where a thiol is to be glycosylated, the acceptor alcohol is in short supply or results are not satisfactory, the thiomethyl glycoside donor may first be converted to the bromo sugar or imidate, and these donors used for glycosylation. Alternatively, glycosylation can be effected with the fully protected precursor e.g. K-2, if significant side reaction is observed with the free hydroxy donors e.g. K-3, K-4, G-4.

In a typical proceedure, 1 mmol of donor (eg G-4, K-2, K-3, K-4, A-6, B-4, C-1 etc) is dissolved in anhydrous dichloromethane 8 mL and an equal weight of dry 4A molecular sieves is added. The mixture is stirred for 30 minutes at room temperature then 4 mmol of the acceptor alcohol is added followed by addition of DMTST solution (6 equivalents in 12ml of DCM). The reaction is monitored by t.l.c. When the reaction is complete, triethylamine (1.2 mmol) is added. The mixture is diluted with 100 mL dichloromethane and extracted with sodium bicarbonate (10% aqueous), citric acid (10% aqueous) and sodium chloride (sat. solution), dried over magnesium sulfate and solvents removed in vacuo. The crude material is chromatographed on silica gel prior to immobilisation or in the case of K-2 removal of one of the alcohol protecting groups.

In an alternative proceedure, 1 mmol of donor in dichloromethane 8 mL is first treated with bromine to yield the crude sugar halide. This solution is washed breifly with 5% sodium thiosulfate, dried over magnesium sulfate and the solvents removed in vacuo. The crude sugar halide is used directly as above with silver triflate as the activating agent in place of DMTST. Both alcohols and thiols are amenable to glycosylation by this method.

Example N: Immobilization onto solid phase

Wang resin (13.3 g; 0.85 mmol/g, p-Benzyloxybenzyl Alcohol polystyrene-divinylbenzene resin) was dried in the vacuum oven overnight in 500 ml round bottom flask. The flask was place under nitrogen atmosphere then dry DCM (133 ml) and trichloroacetonitrile (20 ml) was added. The mixture was cooled with ice bath while gently stirred. After 15 minutes of cooling DBU (1.3 ml) was added drop wise in 15 minutes, the resulting mixture was stirred for one hour with ice bath cooling. The resin was collected by filtering, washed with DMF, THF and DCM (3x each). The resin was dried in the vacuum oven over P_2O_5 for 24 hours to afford 15 grams of TriChloroAcetimidate Wang (TCA-Wang) resin. The resin was packed under nitrogen and stored at 4°C.

Yield 100%; loading *ca.* 0.754 mmol/g.

(Alternative resins may be used).

Glycosylated building blocks containing one free hydroxyl are immobilised onto TCA-Wang resin. In a typical proceedure, TCA Wang resin (3.6 gram) was dried in vacuum oven overnight then washed with anhydrous THF (3x36 ml) under nitrogen atmosphere. Building block (3 equiv.) was added followed by addition of anhydrous DCM (18 ml). The reaction mixture was shaken for 5 minutes (until all alcohol was dissolved), and $BF_3.Et_2O$ (0.35 ml, 1 equvalent) was added. The reaction mixture was shaken vigorously for ten minutes and drained; the resin was washed with DCM (3x30 ml), DMF (3x30 ml), THF (3x30 ml) and dried.

Part C: Library preparation:

The compounds of the invention are prepared by sequential deprotection and ligation chemistries either on solid support or in solution phase. The following typical chemistries may be employed as required.

Removal of a tert-butyldiphenylsilyl:

The resin bound building block is suspended in dry THF/methanol (20/1 v/v) mixture containing 10 equivalents of tetra-n-butylammonium fluoride. The mixture is stirred at 65°C for 24 hours, drained; the resin is filtered, washed with dimethylformamide followed by THF and finally dichloromethane. In an alternative procedure, TBAF may be conveniently replaced by HF.pyridine and the reaction effected in plastic ware. The TBAF may also be replaced by HF."proton sponge" complex with good results.

Removal of a benzoate, p-chlorobenzoate or other ester protecting group:

The resin bound building block is suspended in dry THF and methanol (3/1 v/v) mixture and sodium methoxide (0.5 equivalents) is added. The mixture is shaken for 24 hours, drained and re-treated with fresh reagents for further 24 hours. The resin is filtered, washed with dimethylformamide followed by THF and finally dichloromethane.

Removal of a p-methoxybenzyl group:

The resin bound building block is suspended in DCM and a small amount of water is added (approx 1%) followed by 2,3-dichloro-5,6-dicyanobenzoquinone (10 equivalents). The mixture is shaken for 3 hours drained and re-treated with fresh reagent for a further 3 hours. The resin is filtered, washed with THF followed by methanol and finally dichloromethane.

Etherification of hydroxyl position:

Resin bound building block which has previously had a hydroxyl group deprotected is washed three times and then suspended in anhydrous DMF and 3 equivalents of potassium t-butoxide added (alternative bases may be employed), shaken and drained after 5 minutes followed by the alkylating agent (3 equivalents) in DMF. The mixture is shaken for 10 minutes, drained and re-treated twice more with fresh reagents as above. The resin is filtered, washed with dimethylformamide followed by THF and finally dichloromethane.

Reduction of an azide:

The resin bound building block is suspended in dry DMF; 5 equivalents of DTT (1,4-dithio-DL-threitol) and 3 equivalents of potassium tert-butoxide (alternative bases may be employed) are added. The mixture is agitated under nitrogen atmosphere for 24 hours, drained and the resin is washed with dimethylformamide followed by THF and finally dichloromethane.

Removal of a DTPM group:

The resin bound building block is suspended in DMF and hydrazine hydrate (50/1 v/v) mixture, agitated 2 hours, drained and the resin is washed with dimethylformamide followed by THF and finally dichloromethane

Amide formation:

A solution of a suitable carboxylic acid (10 equivalents) in dry DMF is treated with HBTU (10 equivalents) and di-isopropylethylamine (10 equivalents) and shaken for 5 minutes. This solution is then added to a suspension of Resin

bound building block, which has previously had an amine group deprotected in DMF and the mixture shaken for 30 minutes. After this time the resin is drained and treated once more with fresh reagent for 30 minutes. The resin is filtered, washed with DMF followed by methanol and finally dichloromethane. If desired, quantitative ninhydrin assay may be performed to determine that the reaction is complete. Alternative coupling systems including HOAT, EDC/NHS or anhydrides may be employed to similar effect.

Urea and thiourea formation:

Isocyanates and thioisocyanates may be purchased or prepared by reaction of the corresponding amine with triphosgene, diphosgene, phosgene or thiophosgene as appropriate according to standard procedures as outlined in "Organic Functional Group Preparation" Vol I, 2nd Ed., Sandler and Karo, Academic Press, ISBN:0-12-618601-4 pp 359 to 375.

Resin bound building block which has previously had an amine group deprotected is suspended in anhydrous THF and 2 equivalents of the isocyanate or thioisocyanate added, followed immediately by triethylamine (1 equivalent). The mixture is shaken for 2 hours and may be exothermic depending on the scale and reactivity of the isocyanate or thioisocyanate used, drained and re-treated with fresh reagents for a further 2 hours. The resin is filtered, washed with THF followed by methanol and finally dichloromethane.

Carbamate formation:

Chloroformates and imidoylformates may be purchased or prepared by reaction of the corresponding alcohol with phosgene or carbonylbisimidazole as appropriate according to standard procedures as outlined in "Organic Functional Group Preparation" Vol I, 2nd Ed., Sandler and Karo, Academic Press, ISBN:0-12-618601-4 pp 359 to 375.

Resin bound building block which has previously had an amine group deprotected is suspended in anhydrous THF and 2 equivalents of the

chloroformate or imidoylformate added, followed immediately by triethylamine (1 equivalent). The mixture is shaken for 2 hours and may be exothermic depending on the scale and reactivity of the isocyanate or thioisocyanate used, drained and re-treated with fresh reagents for a further 2 hours. The resin is filtered, washed with THF followed by methanol and finally dichloromethane.

Sulfonamide formation:

Resin bound building block which has previously had an amine group deprotected is suspended in anhydrous THF or DMF and 2 equivalents of the sulfonyl chloride added, followed immediately by triethylamine (2 equivalent). The mixture is shaken for 2 hours, drained and re-treated with fresh reagents for a further 2 hours. The resin is filtered, washed with THF or DMF followed by methanol and finally dichloromethane.

Removal of Fmoc:

The resin bound building block is suspended in piperidine /DMF (1/4, v/v) mixture and stirred 1 hours, drained and repeated once more; the resin is filtered, washed with dimethylformamide followed by THF and finally dichloromethane.

Guanidine formation:

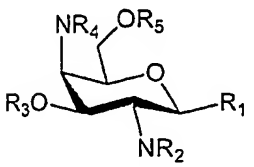
The resin bound building block is suspended in dry DMF containing 3 equivalents of 3,5-dimethylpyrazolyl formamidinium nitrate and 15 equivalents of DIPEA. The mixture is stirred at 65°C for 24 hours, drained; the resin is filtered, washed with dimethylformamide followed by THF and finally dichloromethane.

Cleavage of resin bound product:

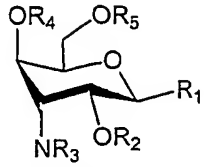
The resin bound compound is suspended in dry DCM containing 20% TFA and 20% Et_3SiH. The mixture is stirred at RT for 3 hours and the aliquot was collected; the resin was washed with dry DCM and all the DCM solutions were

combined, evaporated to dryness under reduced vacuo to furnish the desired product.

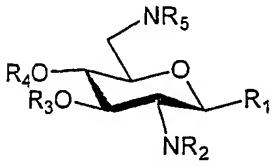
Libraries of compounds of the invention have been prepared based on the following scaffolds:



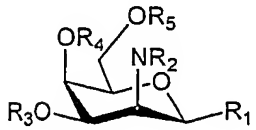
Scaffold **W1** derived from A-6



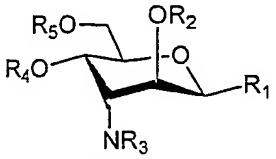
Scaffold **W2** derived from B-4 or K-8



Scaffold **W3** derived from C-1

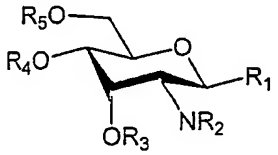


Scaffold **W4** derived from D-5 or I-6

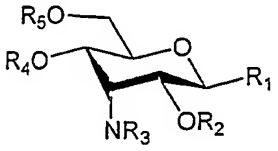


Scaffold **W5** derived from E-9 & E-7

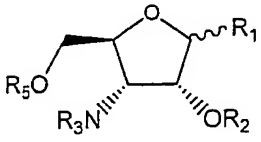
Scaffold **W6** derived from F-5 or F-7



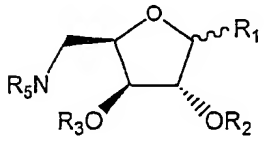
Scaffold **W7** derived from G-4



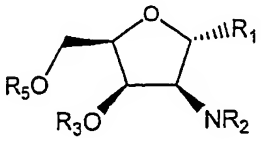
Scaffold **W8** derived from H-9



Scaffold **W9** derived from J-4

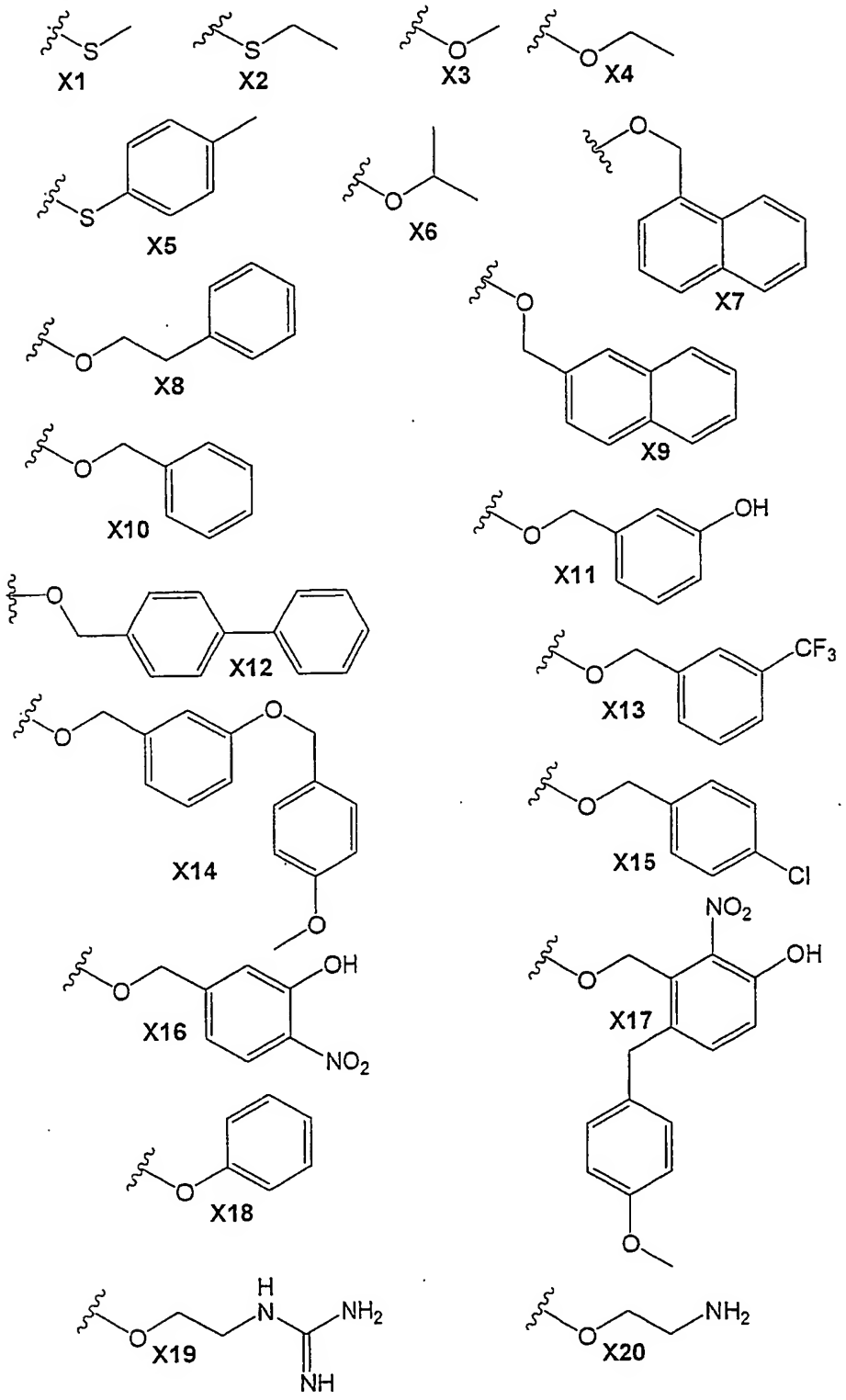


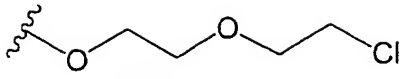
Scaffold **W10** derived from J-6



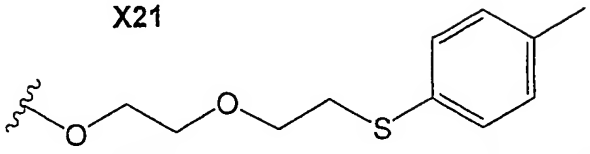
Scaffold **W11** derived from J-7

The following groups are exemplary of moieties in position R1, where the wavey line indicates the point of attachment to the carbohydrate ring:

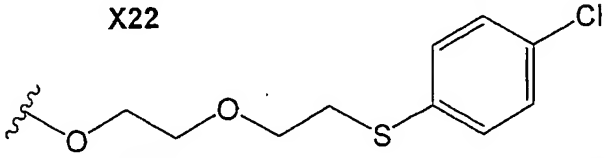




X21



X22



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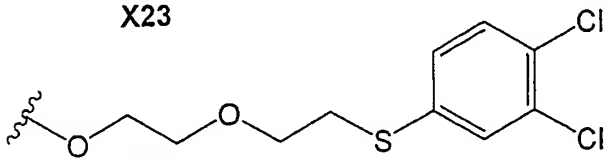
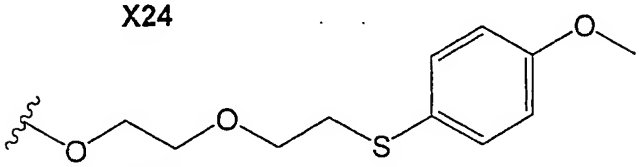
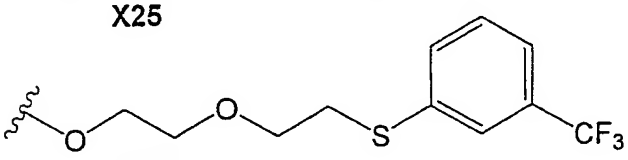


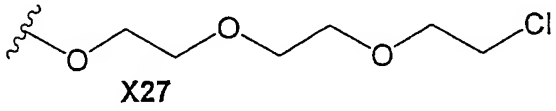
X24



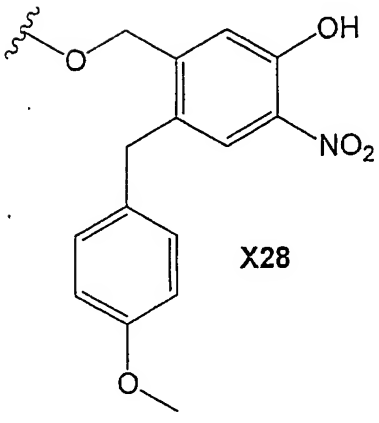
X25



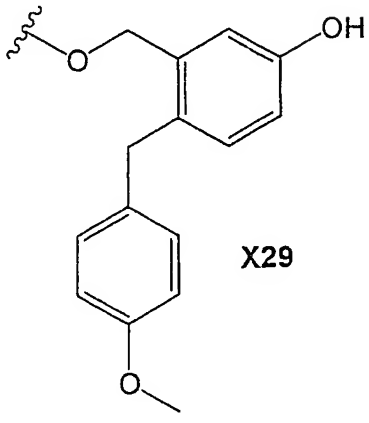
X26



X27



X28



X29

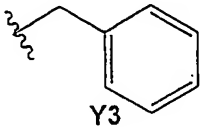
The following groups are exemplary of ether linked moieties, where the wavey line indicates the point of attachment to an oxygen on the carbohydrate ring:

Methyl

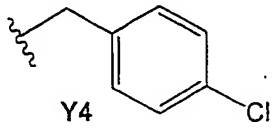
Y1

Ethyl

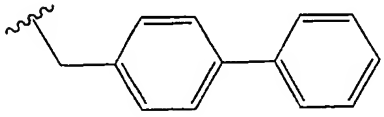
Y2



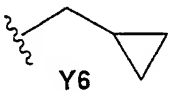
Y3



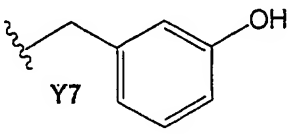
Y4



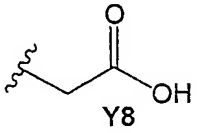
Y5



Y6



Y7



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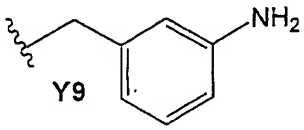

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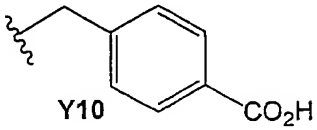

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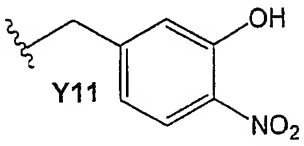

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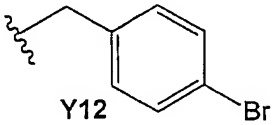

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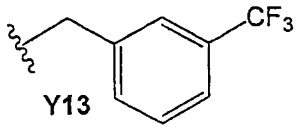

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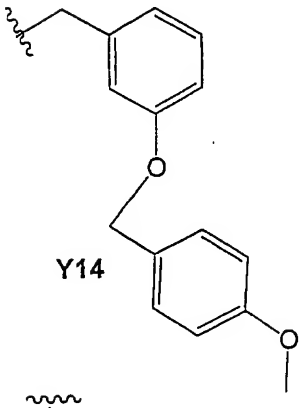

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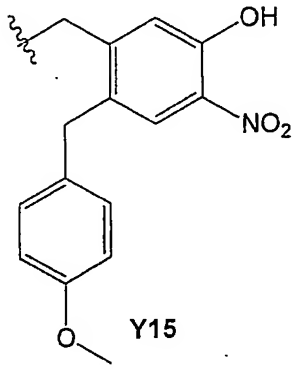

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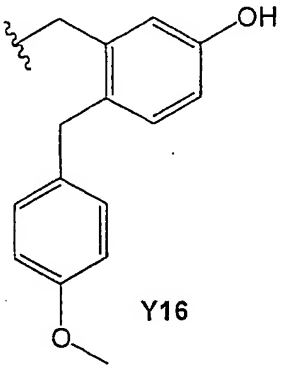

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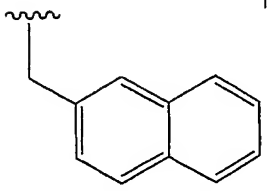

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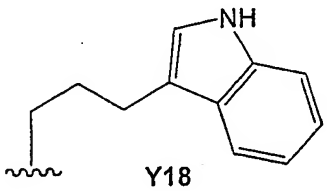

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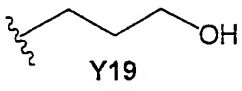

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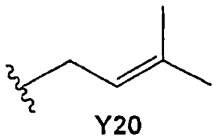
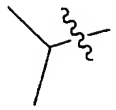
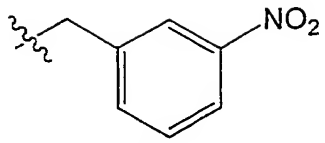


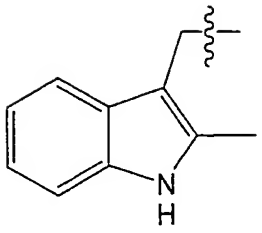
Y20

Octyl





Y21 Y22 Y23



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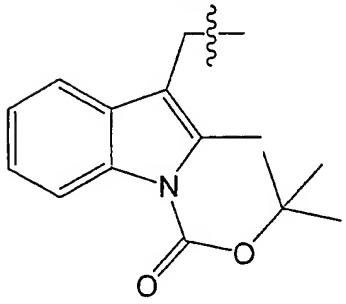

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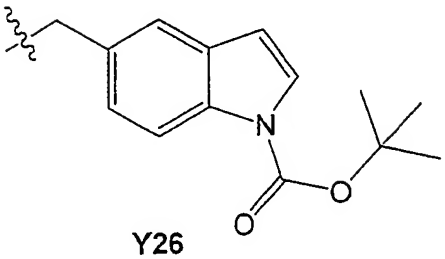

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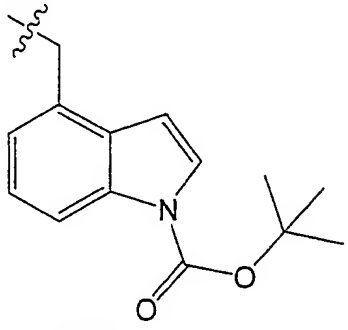

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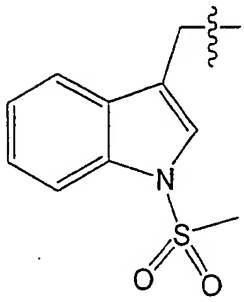

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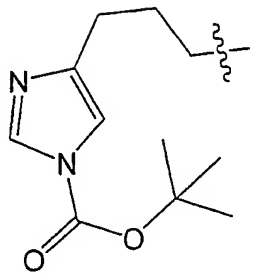

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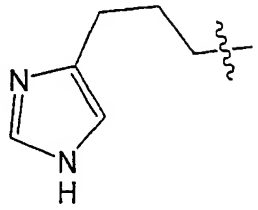
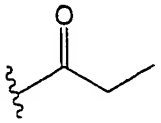
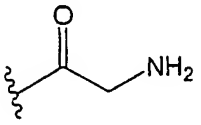


Y30

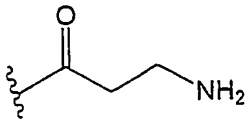
The following groups are exemplary of amine linked moieties, where the wavey line indicates the point of attachment to a nitrogen on the carbohydrate ring:



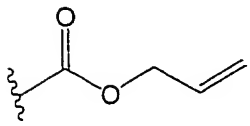
Z1



Z2



Z3



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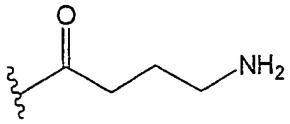

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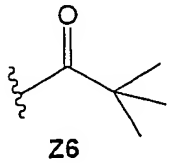

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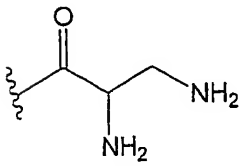

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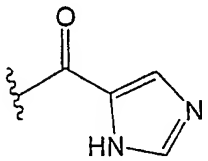

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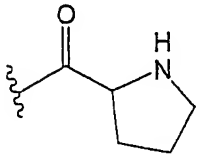

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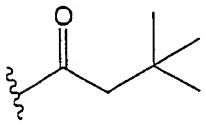

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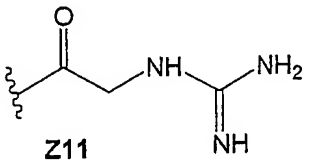

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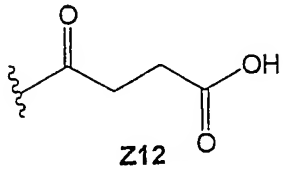

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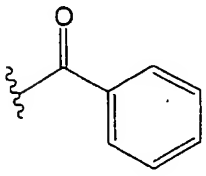

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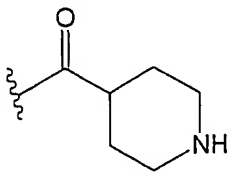

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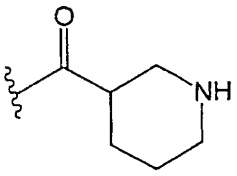

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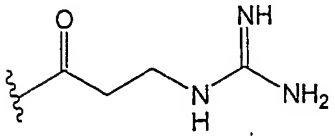

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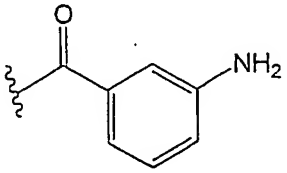

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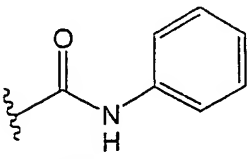

Z18

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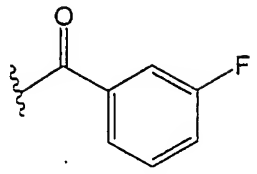

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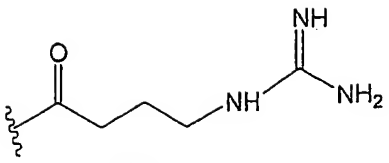

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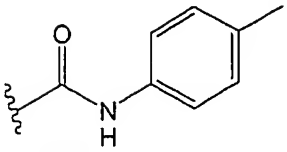

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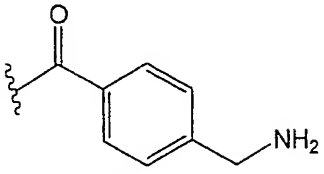

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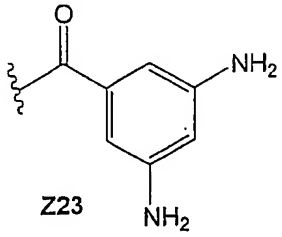

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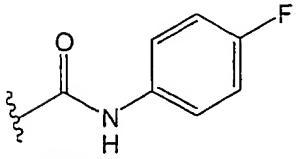

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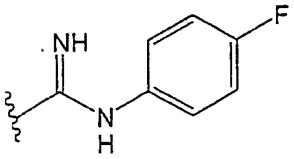

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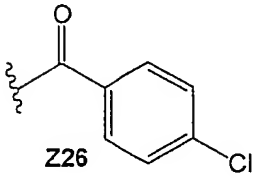

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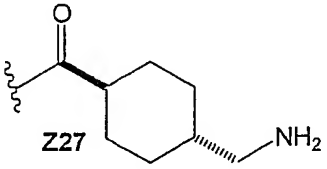

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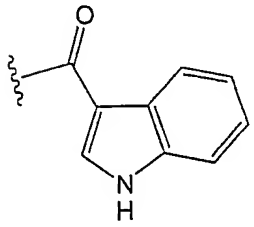

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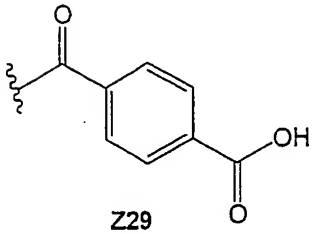

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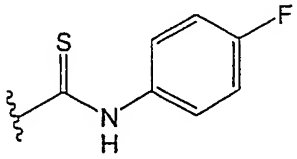

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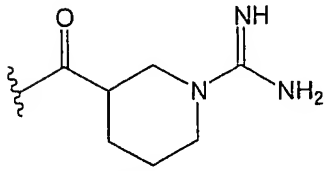

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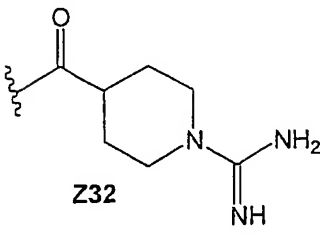

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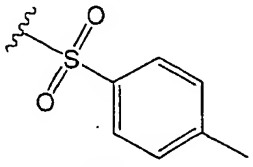

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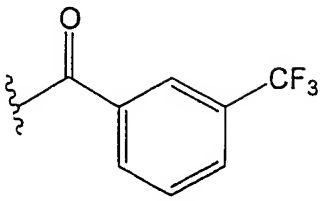

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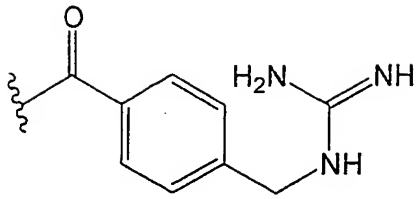
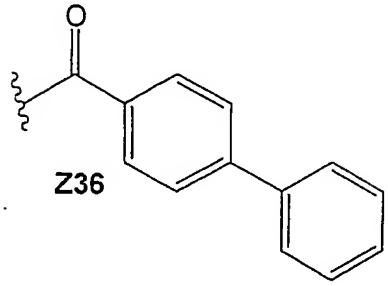


Z35



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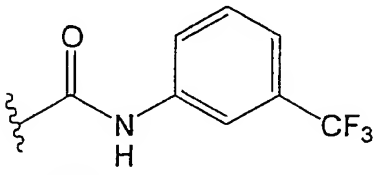

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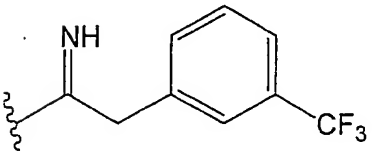

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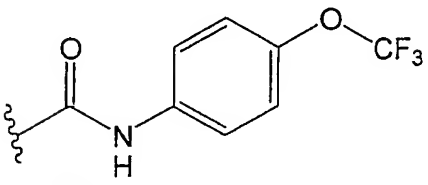

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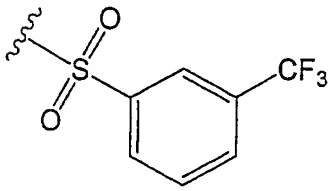

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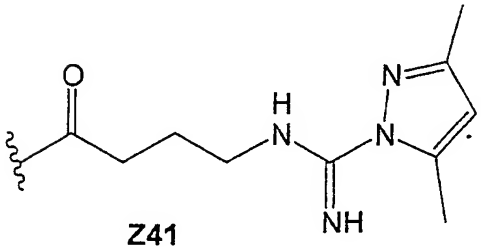

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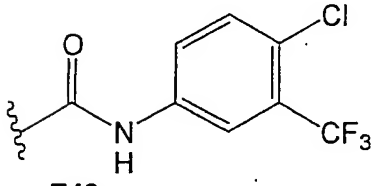

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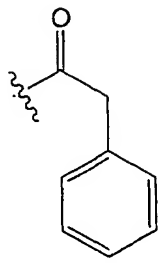

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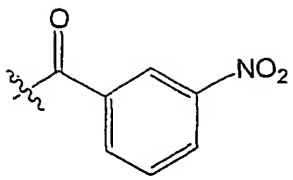

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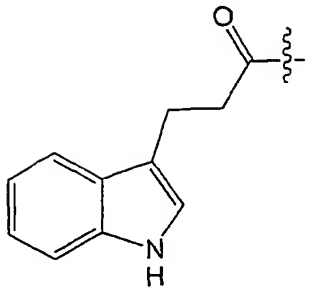

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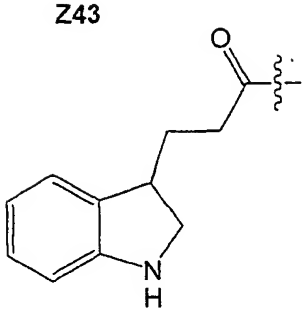

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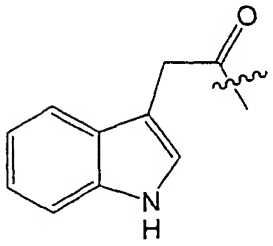

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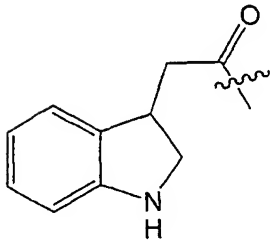

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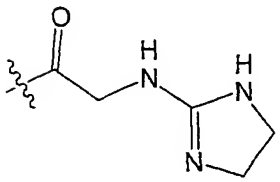

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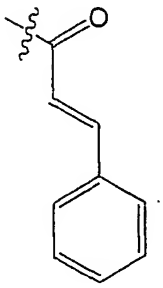

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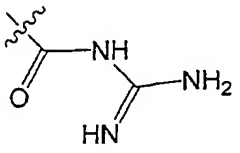

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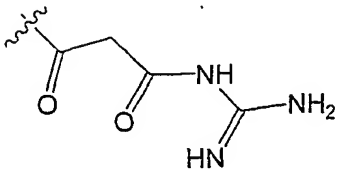

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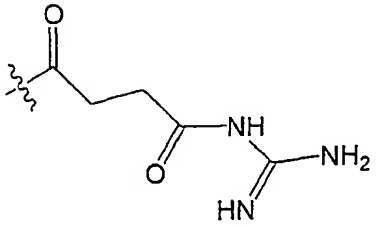

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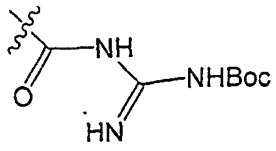

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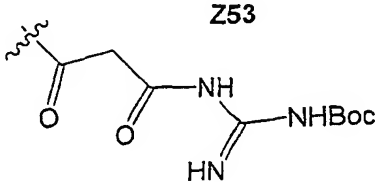

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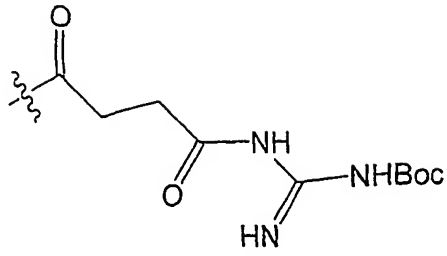

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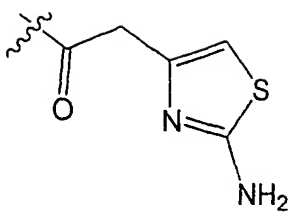

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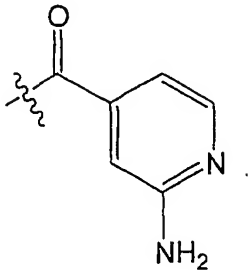

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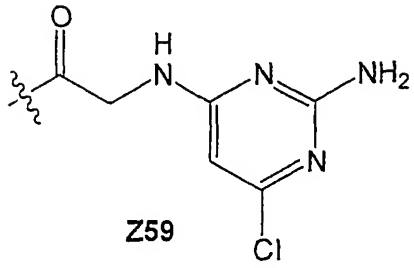

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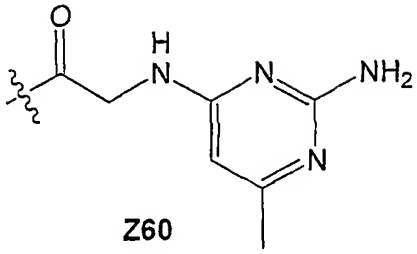

Z60

Exemplary library compounds:

Compound Number	Scaffold	R1	R2	R3	R4	R5
1	W6	X1	Z43	Y3	OH	Y21
2	W6	X1	Z44	Y3	OH	Y22
3	W6	X1	Z45	Y3	OH	Y23
4	W6	X1	Z46	Y3	OH	Y24
5	W6	X1	Z47	Y3	OH	Y25
6	W6	X1	Z48	Y3	OH	Y26
7	W6	X1	Z49	Y3	OH	Y27
8	W6	X1	Z50	Y3	OH	Y28
9	W6	X1	Z51	Y3	OH	Y29
10	W6	X1	Z52	Y3	OH	Y30
11	W6	X1	Z53	Y3	OH	Y21
12	W6	X1	Z54	Y3	OH	Y22
13	W6	X1	Z55	Y3	OH	Y23
14	W6	X1	Z56	Y3	OH	Y24
15	W6	X1	Z57	Y3	OH	Y25
16	W6	X1	Z58	Y3	OH	Y26
17	W6	X1	Z59	Y3	OH	Y27
18	W6	X1	Z60	Y3	OH	Y28
19	W6	X3	Z12	Y9	OH	Y29
20	W6	X3	Z29	Y9	OH	Y30
21	W6	X3	Z12	Y9	OH	Y12
22	W6	X3	Z29	Y9	OH	Y12
23	W6	X3	Z13	Y9	OH	Y8
24	W6	X3	Z26	Y9	OH	Y8
25	W6	X3	Z13	Y3	OH	Y10
26	W6	X3	Z26	Y3	OH	Y10
27	W6	X4	Z3	Y3	OH	Y8
28	W6	X4	Z17	Y3	OH	Y8

29	W6	X4	Z3	Y3	OH	Y10
30	W6	X4	Z17	Y3	OH	Y10
31	W6	X4	Z12	Y3	OH	Y9
32	W6	X4	Z29	Y3	OH	Y9
33	W6	X4	Z3	Y12	OH	Y8
34	W6	X4	Z17	Y12	OH	Y8
35	W6	X4	Z3	Y12	OH	Y10
36	W6	X4	Z17	Y12	OH	Y10
37	W6	X4	Z12	Y12	OH	Y9
38	W6	X4	Z29	Y12	OH	Y9
39	W6	X4	Z3	Y8	OH	Y3
40	W6	X4	Z17	Y8	OH	Y3
41	W6	X4	Z3	Y8	OH	Y12
42	W6	X4	Z17	Y8	OH	Y12
43	W6	X4	Z13	Y8	OH	Y9
44	W6	X4	Z26	Y8	OH	Y9
45	W6	X4	Z3	Y10	OH	Y3
46	W6	X4	Z17	Y10	OH	Y3
47	W6	X4	Z3	Y10	OH	Y12
48	W6	X4	Z17	Y10	OH	Y12
49	W6	X4	Z13	Y10	OH	Y9
50	W6	X4	Z26	Y10	OH	Y9
51	W6	X4	Z12	Y9	OH	Y3
52	W6	X4	Z29	Y9	OH	Y3
53	W6	X4	Z12	Y9	OH	Y12
54	W6	X4	Z29	Y9	OH	Y12
55	W6	X4	Z13	Y9	OH	Y9
56	W6	X4	Z26	Y9	OH	Y9
57	W6	X4	Z13	Y9	OH	Y10
58	W6	X4	Z26	Y9	OH	Y10
59	W6	X4	Z3	Y2	OH	Y8

60	W6	X4	Z17	Y2	OH	Y8
61	W6	X4	Z3	Y2	OH	Y10
62	W6	X4	Z17	Y2	OH	Y10
63	W6	X4	Z12	Y2	OH	Y9
64	W6	X4	Z29	Y2	OH	Y9
65	W6	X4	Z3	Y8	OH	Y1
66	W6	X10	Z17	Y8	OH	Y1
67	W6	X10	Z3	Y8	OH	Y2
68	W6	X10	Z17	Y8	OH	Y2
69	W6	X10	Z1	Y8	OH	Y9
70	W6	X10	Z4	Y8	OH	Y9
71	W6	X10	Z3	Y10	OH	Y1
72	W6	X10	Z17	Y10	OH	Y1
73	W6	X10	Z3	Y10	OH	Y2
74	W6	X10	Z17	Y10	OH	Y2
75	W6	X10	Z1	Y10	OH	Y9
76	W6	X10	Z4	Y10	OH	Y9
77	W6	X10	Z12	Y9	OH	Y1
78	W6	X10	Z29	Y9	OH	Y1
79	W6	X10	Z12	Y9	OH	Y2
80	W6	X10	Z29	Y9	OH	Y2
81	W6	X10	Z1	Y9	OH	Y9
82	W6	X10	Z4	Y9	OH	Y9
83	W6	X15	Z11	Y1	OH	Y17
84	W6	X15	Z4	Y9	OH	Y10
85	W8	X6	Y8	Z33	OH	Y9
86	W8	X6	Y10	Z24	OH	Y19
87	W8	X6	Y7	Z18	OH	Y12
88	W8	X9	Y9	Z25	OH	Y3
89	W8	X9	Y19	Z1	OH	Y4
90	W8	X9	Y12	Z20	OH	Y13

91	W8	X12	Y3	Z25	OH	Y17
92	W8	X12	Y4	Z20	OH	Y11
93	W8	X12	Y13	Z20	OH	Y18
94	W8	X10	Y17	Z36	OH	Y8
95	W8	X10	Y11	Z42	OH	Y10
96	W8	X10	Y18	Z18	OH	Y13
97	W1	X6	Z33	Y4	Z37	OH
98	W1	X6	Z37	OH	Z33	Y3
99	W1	X6	Z42	OH	Z18	Y3
100	W1	X9	Z33	Y4	Z37	OH
101	W1	X9	Z37	OH	Z33	Y3
102	W1	X9	Z42	OH	Z18	Y3
103	W1	X12	Z33	Y4	Z37	OH
104	W1	X12	Z37	OH	Z33	Y3
105	W1	X12	Z42	OH	Z18	Y3
106	W6	X12	Z11	Y5	OH	Y1
107	W6	X12	Z16	Y5	OH	Y1
108	W6	X12	Z5	Y5	OH	Y1
109	W6	X12	Z11	Y17	OH	Y1
110	W6	X12	Z16	Y17	OH	Y1
111	W6	X12	Z5	Y17	OH	Y1
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113	W6	X12	Z16	Y3	OH	Y1
114	W6	X12	Z5	Y3	OH	Y1
115	W6	X12	Z11	Y4	OH	Y1
116	W6	X12	Z16	Y4	OH	Y1
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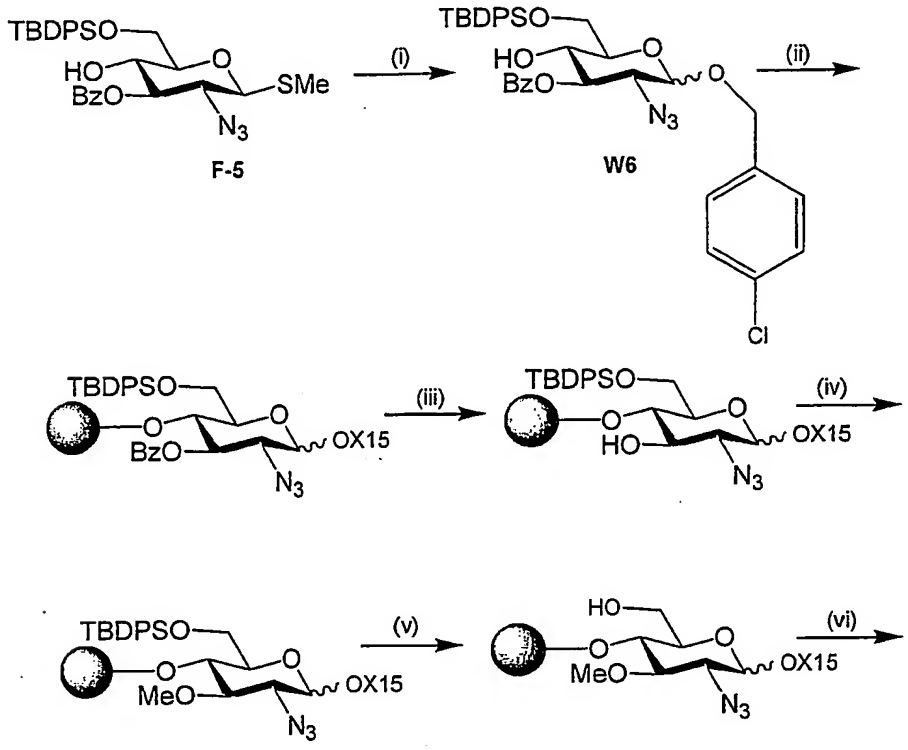
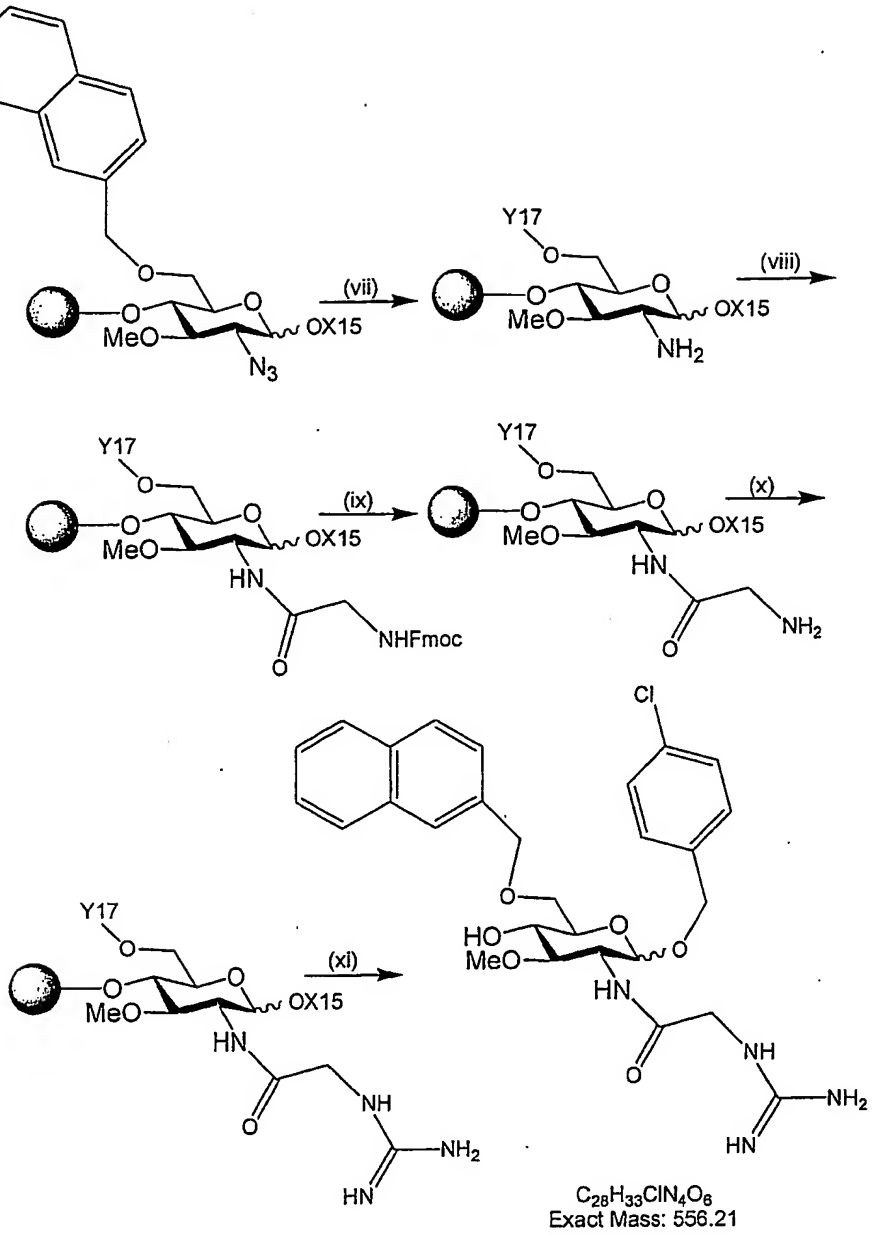
118	W6	X9	Z11	Y5	OH	Y1
119	W6	X9	Z16	Y5	OH	Y1
120	W6	X9	Z5	Y5	OH	Y1
121	W6	X9	Z11	Y17	OH	Y1

122	W6	X9	Z16	Y17	OH	Y1
123	W6	X9	Z5	Y17	OH	Y1
124	W6	X9	Z11	Y3	OH	Y1
125	W6	X9	Z16	Y3	OH	Y1
126	W6	X9	Z5	Y3	OH	Y1
127	W6	X9	Z11	Y4	OH	Y1
128	W6	X9	Z16	Y4	OH	Y1
129	W6	X9	Z5	Y4	OH	Y1
130	W6	X12	Z11	Y1	OH	Y5
131	W6	X12	Z16	Y1	OH	Y5
132	W6	X12	Z5	Y1	OH	Y5
133	W6	X19	Z28	Y1	OH	Y3
134	W6	X19	Z13	Y1	OH	Y17
135	W6	X19	Z13	Y17	OH	Y1
136	W6	X3	Z29	Y12	OH	Y9
137	W6	X3	Z17	Y8	OH	Y3
138	W6	X3	Z17	Y8	OH	Y12
139	W7	X12	Z11	Y11	OH	Y1
140	W7	X12	Z16	Y15	OH	Y1
141	W7	X12	Z3	Y16	OH	Y1
142	W7	X8	Z11	Y11	OH	Y1
143	W7	X8	Z16	Y15	OH	Y1
145	W7	X8	Z3	Y16	OH	Y1
146	W7	X15	Z11	Y11	OH	Y1
147	W7	X15	Z16	Y15	OH	Y1
148	W7	X15	Z3	Y16	OH	Y1
149	W7	X17	Z11	Y4	OH	Y1
150	W7	X15	Z7	OH	Y4	Y17
151	W7	X15	Z31	OH	Y4	Y17
152	W7	X15	Z9	OH	Y4	Y17
153	W7	X15	Z32	OH	Y4	Y17

154	W6	X15	Z42	Y6	Y1	OH
155	W6	X15	Z37	Y20	Y1	OH
156	W6	X15	Z39	Y2	Y1	OH
157	W6	X14	Z42	Y6	Y8	OH
158	W6	X14	Z37	Y20	Y8	OH
159	W6	X6	Z17	Y8	Y3	OH
160	W2	X8	OH	Z13	Y4	Y1
161	W2	X8	OH	Z16	Y4	Y1
162	W3	X15	Z36	Y4	OH	Z37
163	W3	X5	Z11	Y4	OH	Z33
164	W3	X5	Z8	Y4	OH	Z24
165	W3	X5	Z36	Y4	OH	Z37
166	W3	X1	Z11	OH	OH	Z33
167	W3	X1	Z8	OH	OH	Z24
168	W3	X1	Z36	OH	OH	Z37
169	W3	X15	Z11	Y4	OH	Z33
170	W3	X15	Z8	Y4	OH	Z24
171	W4	X12	Z10	Y4	Y8	OH
172	W4	X12	Z41	Y8	Y3	OH
173	W5	X8	Y17	Z13	Y4	OH
174	W5	X8	Y17	Z16	Y4	OH
175	W9	X22	Y4	Z3	Absent	OH
176	W9	X23	Y5	Z11	Absent	OH
177	W9	X26	Y8	Z3	Absent	OH
178	W9	X21	Y17	Z11	Absent	OH
179	W10	X3	Y6	OH	Absent	Z25
180	W10	X5	Y12	OH	Absent	Z30
181	W10	X10	Y19	OH	Absent	Z40
182	W11	X6	Z25	OH	Absent	Y6
183	W11	X8	Z30	OH	Absent	Y12
184	W11	X10	Z40	OH	Absent	Y19

Exemplary synthesis of compound 85 (W6-X15-Z11-Y1-OH-Y17) on solid phase.





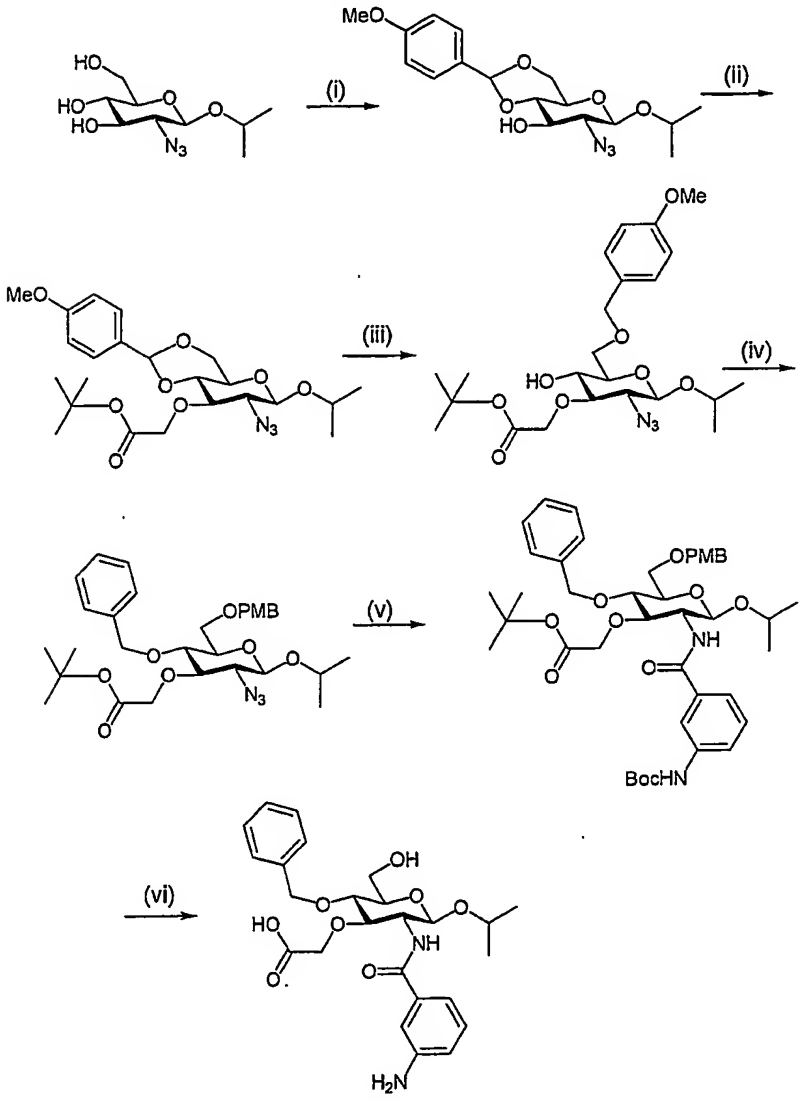
Conditions: (i) a. Br_2, DCM; b. 4-Chlorobenzylalcohol, AgOTf, DCM; (ii) TCA-Wang resin, $BF_3.Et_2O$, DCM, THF; (iii) NaOMe, THF, MeOH; (iv) a. $KOBu^t$, DMF; b. iodomethane, DMF; (v) HF.'proton sponge', AcOH, DMF, 65°C; (vi) a. $KOBu^t$, DMF; b. 2-bromomethyl-naphthalene, DMF; (vii) 1,4-Dithio-DL-threitol, $KOBu^t$, DMF; (viii) HBTU, Fmoc-Gly-OH, DIPEA, DMF; (ix) piperidine/ DMF (1/4); (x) 3,5-dimethylpyrazolyl formamidinium nitrate, DIPEA, DMF; (xi) TFA, Et_3SiH, DCM.

LCMS method:

Time	water%	acetonitrile%	Flow (ml/min)
0.00	95.0	5.0	2.000
1.00	95.0	5.0	2.000
7.00	0.0	100.0	2.000
12.00	0.0	100.0	2.000

M+H = 557.3; Rt = 3.98 min

Exemplary synthesis of compound 159 (W6-Z17-Y8-Y3-OH) in solution phase:

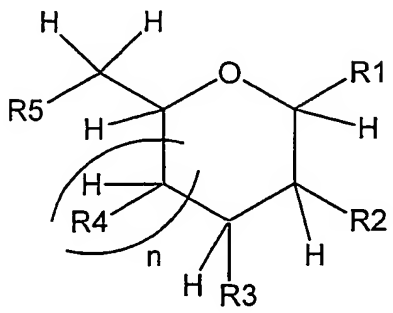


Conditions: (i) 4-Methoxybenzaldehyde dimethylacetal, TsOH, CH_3CN; (ii) NaH (95%), tert-butyl bromoacetate, DMF; (iii) $NaBH_3CN$, TFA, DMF; (iv) $KOBu^t$, BnBr, DMF; (v) a. Zn, NH_4Cl, MeOH, H_2O; b. HBTU, 3-Boc-NH-benzoic acid, DIPEA, DMF; (vi) CH_3CN, H_2O, TsOH.

It should be appreciated that various changes and modifications can be made to the embodiments without departing from the spirit and scope of the invention.

CLAIMS:

1. A compound of formula I being a derivative of a furanose or pyranose form of a monosaccharide,



formula I

Wherein, n is 0 or 1;

R1 is XR wherein,

X is selected from O; S; S=O and SO_2,

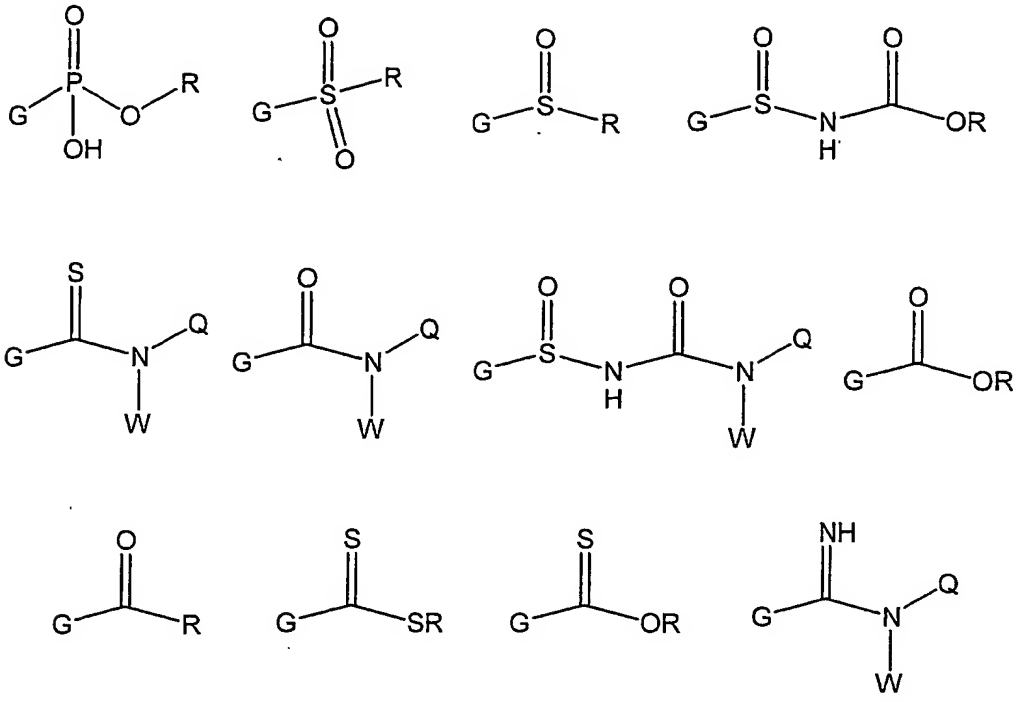
R is selected from the group consisting of C1 to C9 alkyl, C1 to C15 alkenyl, C1 to C15 alkynyl, C1 to C15 heteroalkyl, C6 to C15 aryl, C6 to C15 heteroaryl, C6 to C15 arylalkyl or C6 to C15 heteroarylalkyl which is optionally substituted, cyclic or acyclic, branched and/or linear,

the groups R2 to R5 are selected from OH, OR and N(Y)Z such that:

at least one of the groups R2 to R5 and not more than two of the groups R2 to R5 are OH,

at least one of the groups R2 to R5 and not more than two of the groups R2 to R5 are OR, where R is defined above, with the proviso that when two of the groups R2 to R5 are OR, the R groups may not both be methyl or unsubstituted benzyl,

at least one of the groups R2 to R5 and not more than two of the groups R2 to R5 are N(Y)Z, where Z is selected from hydrogen or R and Y is selected from the following, where G denotes the point of connection to the nitrogen atom in N(Y)Z, the N(Y)Z moieties may not be the same;



and the groups Q and W are independently selected from hydrogen or R as is defined above, and Q and W may combine to form a cycle,

the groups Z and Y may combine to form a cycle,

the groups R1 to R5 may not combine together to form a cycle,

with the proviso that where two groups in the compound of formula I are N(Y)Z, these groups are different,

with the further proviso that when either R2 or R5 is N(Y)Z, N(Y)Z may not be azido, acetyl, benzyloxycarbonyl or t-butoxycarbonyl,

with the further proviso that when R2 is N(Y)Z, N(Y)Z may not be phthalimido, 4-[*N*-[1-(4,4-dimethyl-2,6-dioxocyclo-hexylidene)-3-methylbutyl]-amino}benzyl ester (ODmab), *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde), 2,2,2-Trichloroethoxycarbonyl (Troc), 9-Fluorenylmethoxycarbonyl (Fmoc), or a 5-Acyl-1,3-dimethylbarbiturate type protecting group (DTPM),

with the further proviso that when the scaffold is of the 2-deoxy-2-aminoglucose configuration and R5 and R4 are both hydroxyl, R3 may not be a glycolate [-

CH_2-CO_2H] or lactate ether [-$CH(CH_3)$-CO_2H] or an ester or amide derivative thereof.

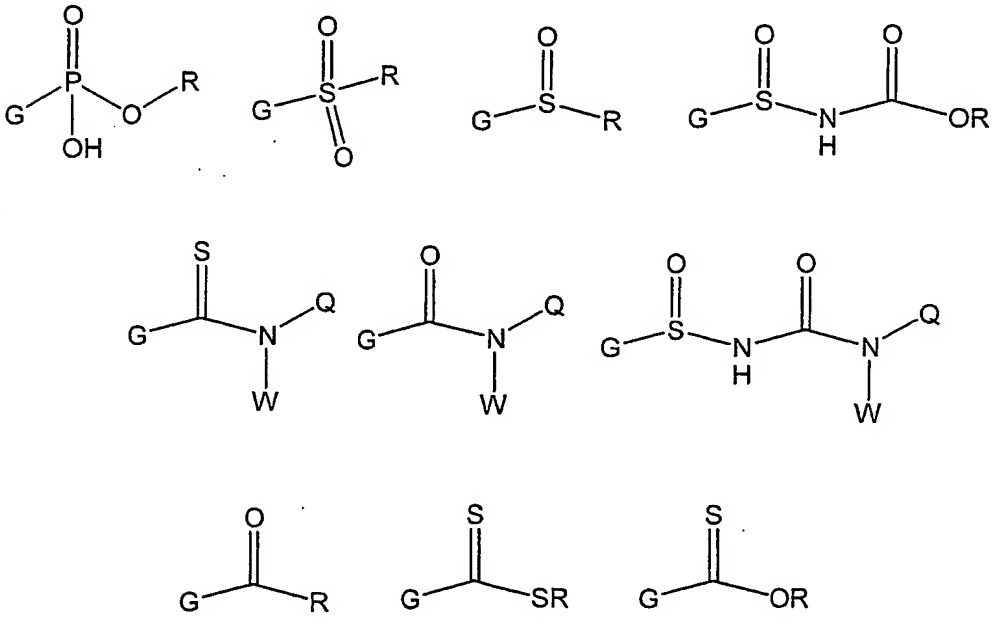
2. The compound of claim 1 which is a derivative of a pyranose form of a monosaccharide and wherein n is 1.

3. The compound of claim 1 which is a derivative of a furanose form of a monosaccharide, and wherein n is 0.

4. The compound of claim 2, wherein

n is 1,

at least one of the groups R2 to R5 and not more than two of the groups R2 to R5 are N(Y)Z, where Z is selected from hydrogen or R and Y is selected from the following, where G denotes the point of connection to the nitrogen atom in N(Y)Z, the N(Y)Z moieties may not be the same;



and the groups Q and W are independently selected from hydrogen or R as is defined above, with the proviso that Y and Z may not both be hydrogen and

where two groups in the compound of formula I are N(Y)Z, these groups are different,

the groups Z and Y may combine to form a cycle,

the groups R1 to R5 may not combine together to form a cycle,

with the proviso that where two groups in the compound of formula I are N(Y)Z, these groups are different,

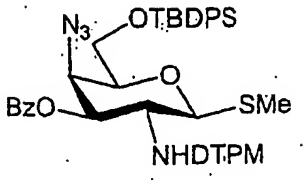
with the further proviso that when either R2 or R5 is N(Y)Z, N(Y)Z may not be azido, acetyl, benzyloxycarbonyl or t-butoxycarbonyl,

with the further proviso that when R2 is N(Y)Z, N(Y)Z may not be phthalimido, 4-[*N*-[1-(4,4-dimethyl-2,6-dioxocyclo-hexylidene)-3-methylbutyl]-amino}benzyl ester (ODmab), *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde), 2,2,2-Trichloroethoxycarbonyl (Troc), 9-Fluorenylmethoxycarbonyl (Fmoc), or a 5-Acyl-1,3-dimethylbarbiturate type protecting group (DTPM),

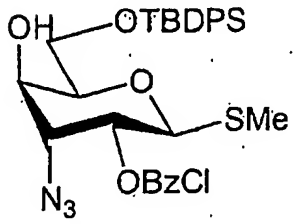
with the further proviso that when the scaffold is of the 2-deoxy-2-aminoglucose configuration and R5 and R4 are both hydroxyl, R3 may not be a glycolate [-CH_2-CO_2H] or lactate ether [-$CH(CH_3)$-CO_2H] or an ester or amide derivative thereof.

5. The compound of any one of claim 1-4 wherein the heteroarylalkyl is substituted by a moiety from the group consisting of OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may be further substituted, with the proviso that the group R may not be or contain another saccharide moiety, a peptide, protein or amino acid.

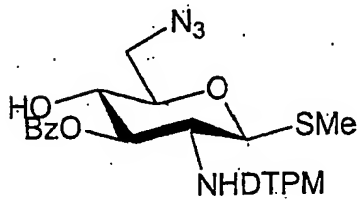
6. The compound of claim 1 which comprises, as a precursor



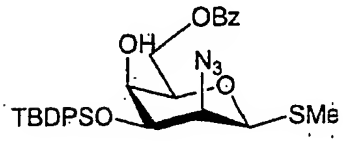
7. The compound of claim 1, which comprises as a precursor



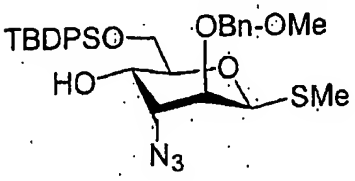
8. The compound of claim 1, which comprises as a precursor



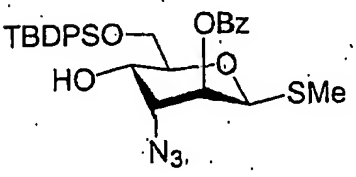
9. The compound of claim 1, which comprises as a precursor



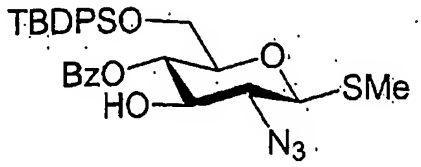
10. The compound of claim 1, which comprises as a precursor



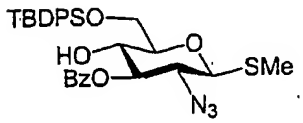
11. The compound of claim 1, which comprises as a precursor



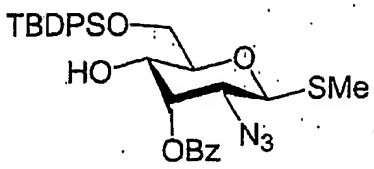
12. The compound of claim 1, which comprises as a precursor



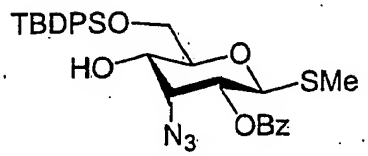
13. The compound of claim 1, which comprises as a precursor



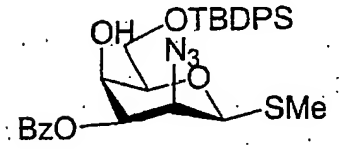
14. The compound of claim 1, which comprises as a precursor



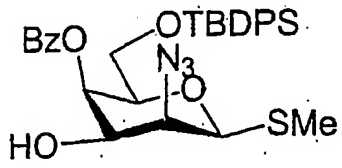
15. The compound of claim 1, which comprises as a precursor



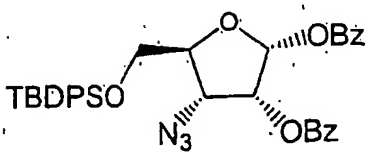
16. The compound of claim 1, which comprises as a precursor



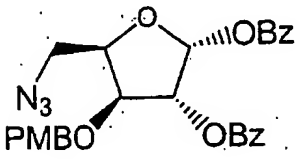
17. The compound of claim 1, which comprises as a precursor



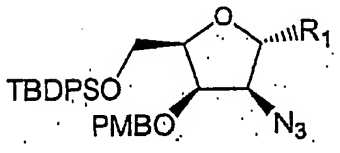
18. The compound of claim 1, which comprises as a precursor



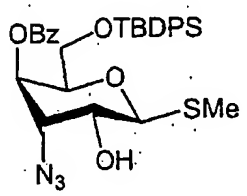
19. The compound of claim 1, which comprises as a precursor



20. The compound of claim 1, which comprises as a precursor



21. The compound of claim 1, which comprises as a precursor

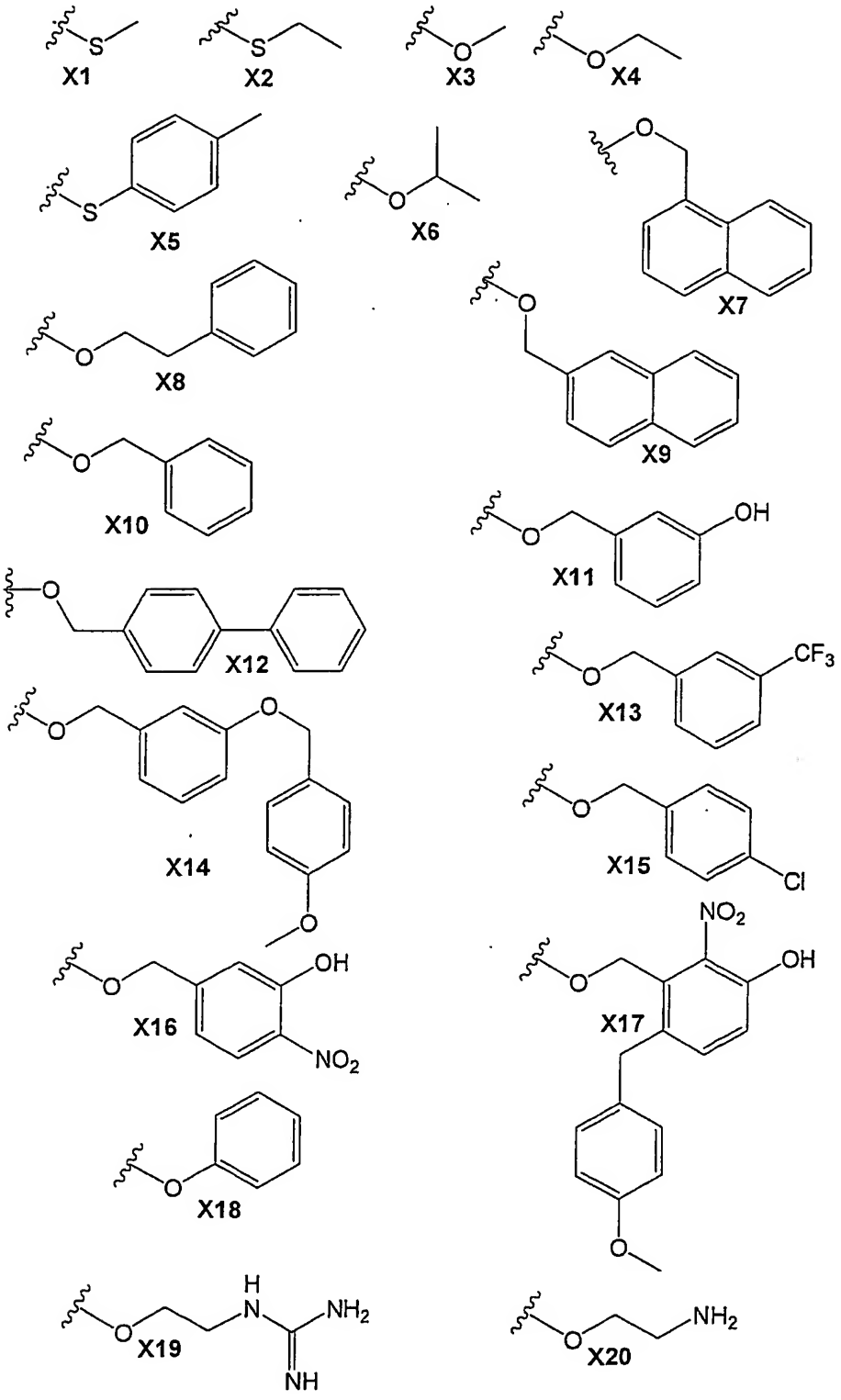


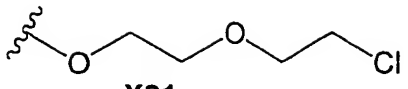
22. The compound of claim 1 which is immobilised to a support.

23. The compound of claim 22, wherein the compound is immobilised to the support through a hydroxyl group.

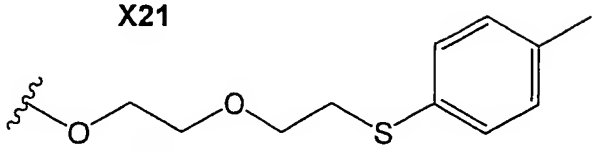
24 The compound of claim 23, wherein the support is selected from the group consisting of derivatised polystyrene, tentagel, wang resin, MBHA resin, aminomethylpolystyrene, rink amide resin , DOX-mpeg and polyethylene glycol.

25. The compound of claim 1, wherein R1 is selected from the group consisting of





X21



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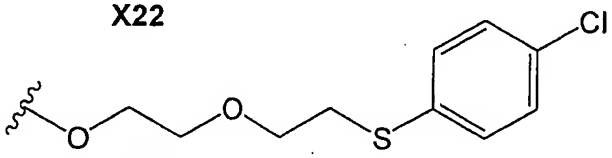

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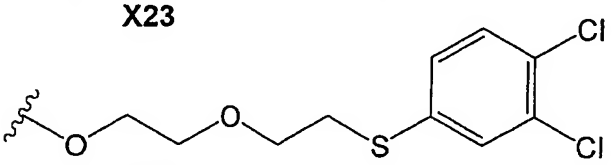

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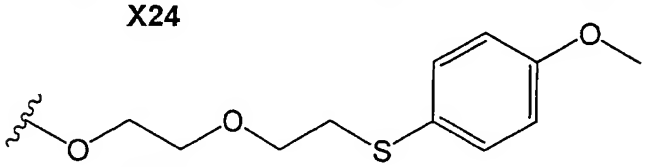

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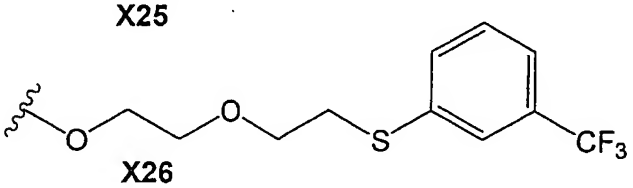
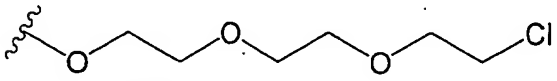
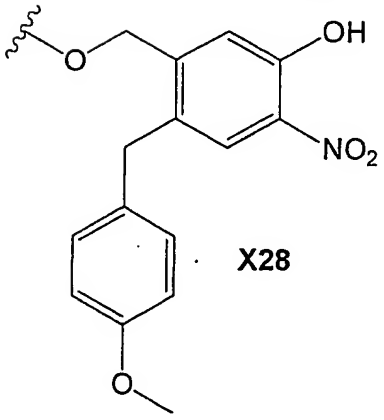


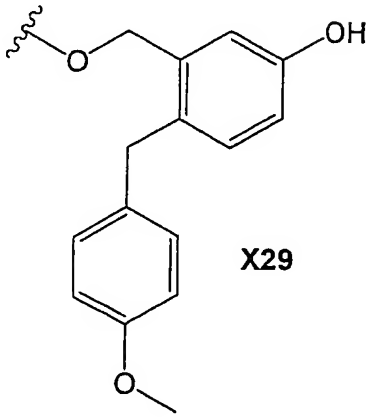
X26



X27



X28

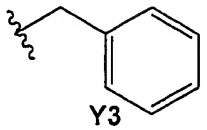


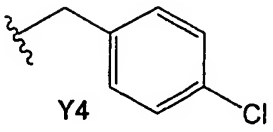
X29

26. The compound of claim 1, wherein one of the R moieties in OR is selected from the group consisting of

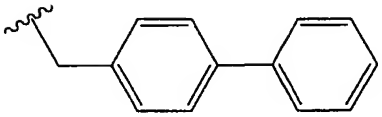
Methyl Y1

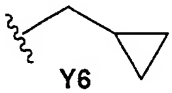
Ethyl Y2

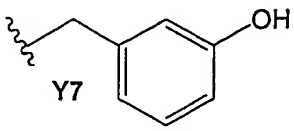

Y3



Y4


Y5


Y6



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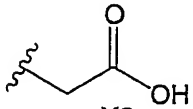
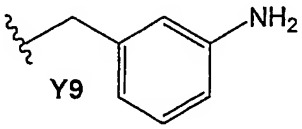
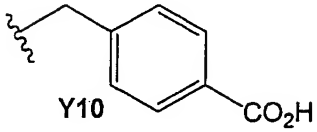


Y8



Y9



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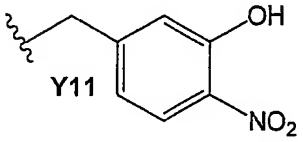

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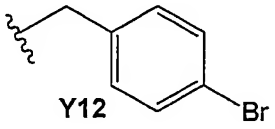

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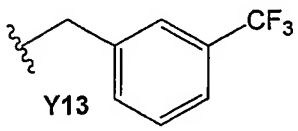

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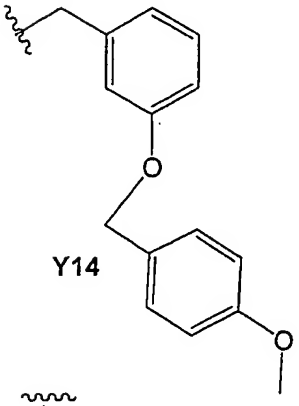
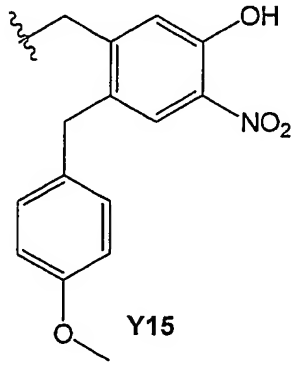


Y14



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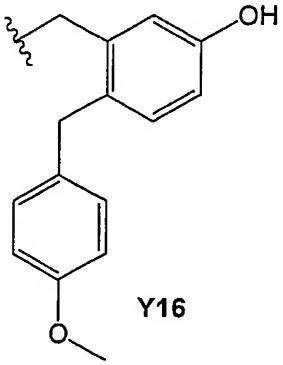
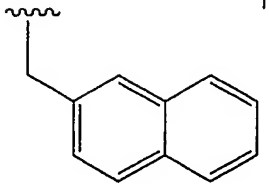


Y16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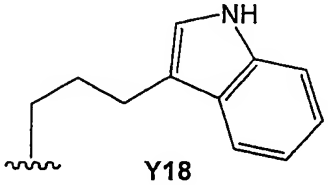

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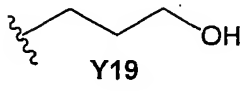

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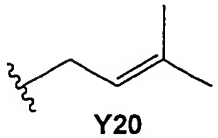
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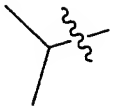
Y21



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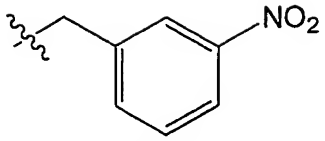

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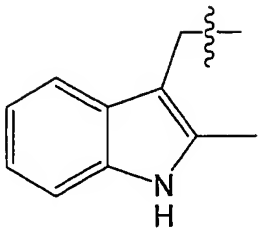

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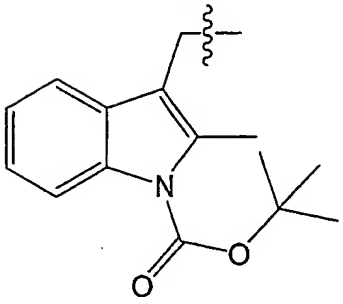

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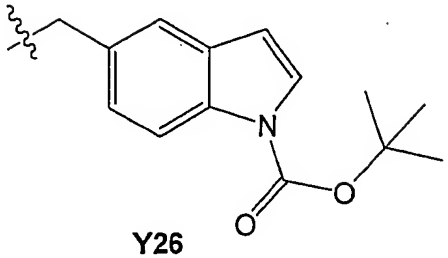

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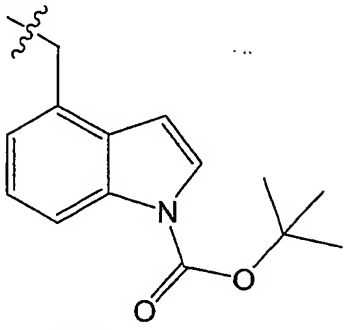

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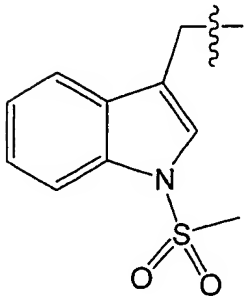

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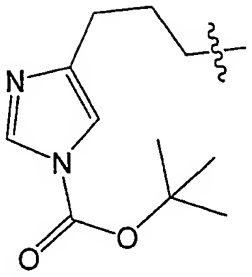

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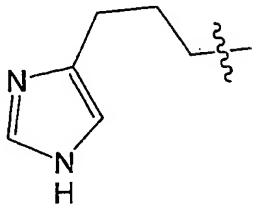
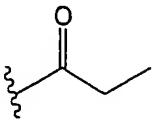
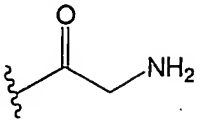


Y30

27. The compound of claim 1, wherein Z is selected from the group consisting of



Z1



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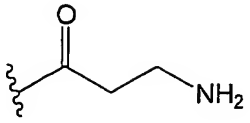

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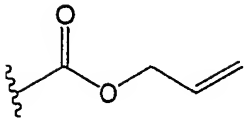

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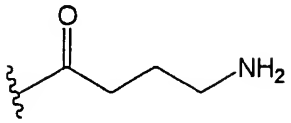

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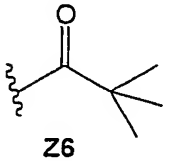

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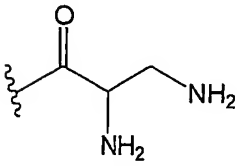

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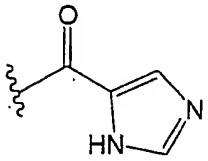

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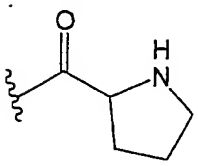

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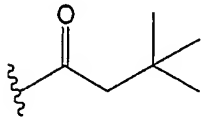

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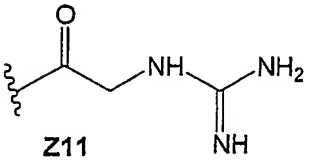

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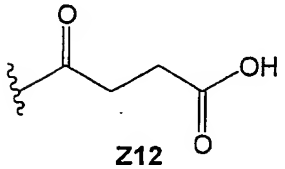

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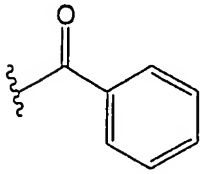

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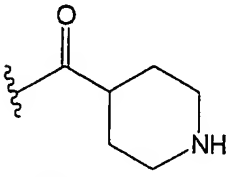

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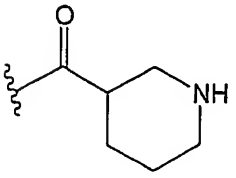

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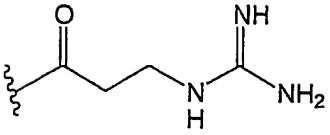

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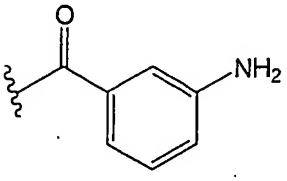

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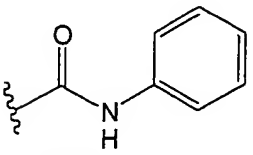

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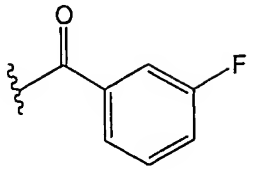

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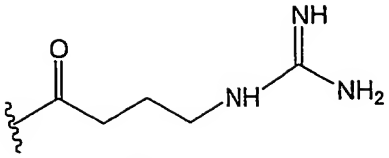

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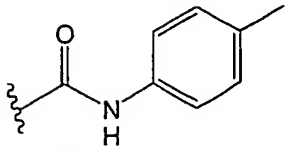

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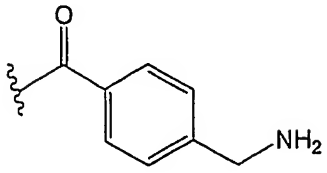

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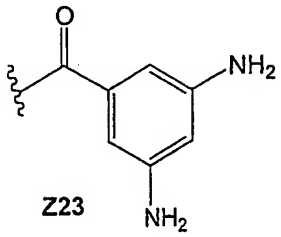

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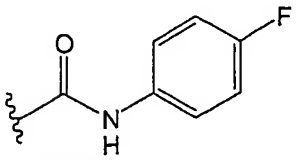

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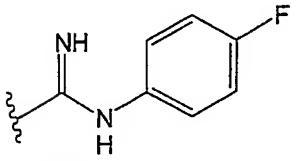

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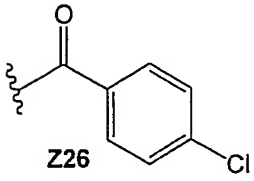

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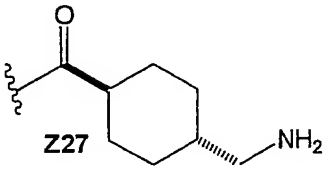

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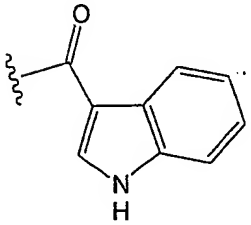

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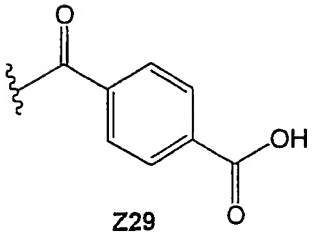

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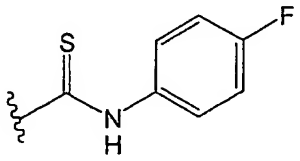

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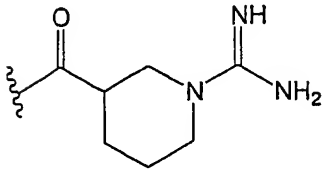

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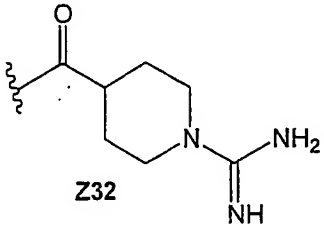

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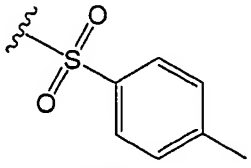

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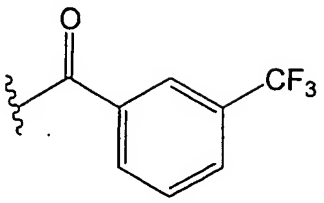

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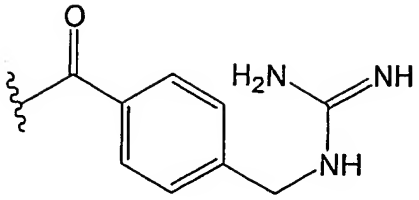

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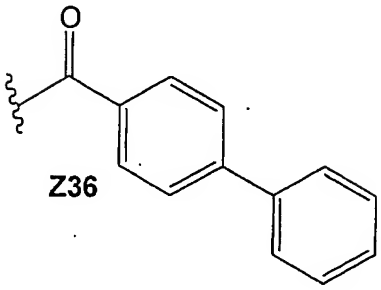

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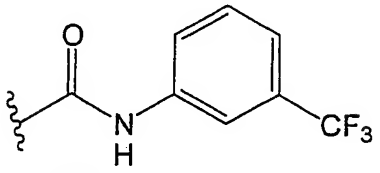

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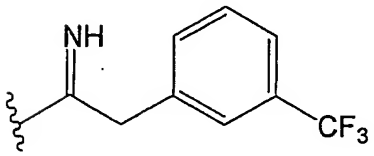

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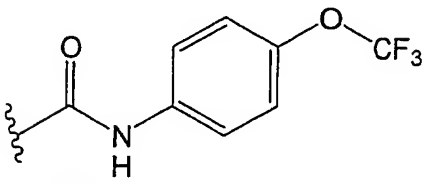

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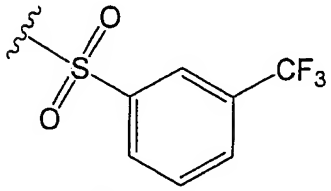

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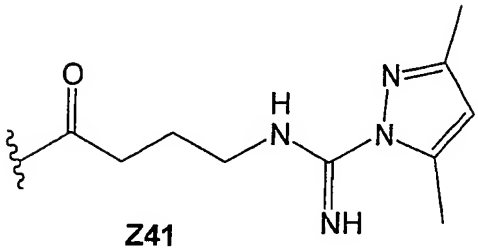

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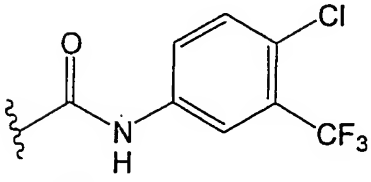

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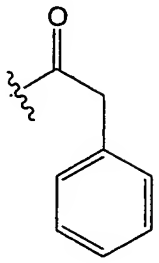

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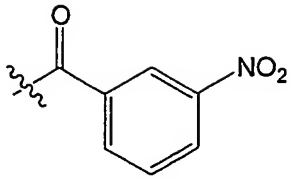

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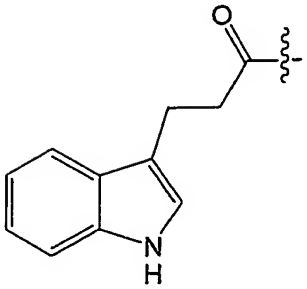

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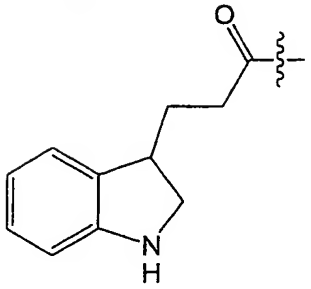

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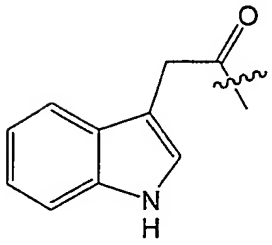

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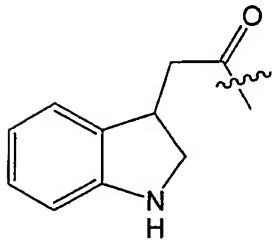

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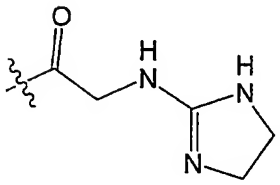

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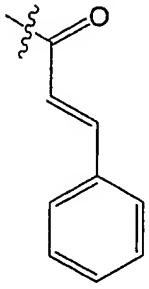

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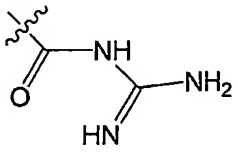

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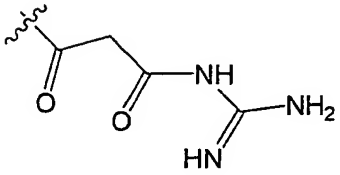

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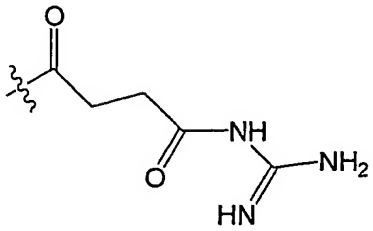

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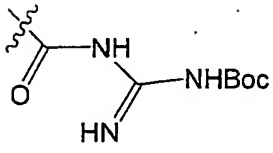

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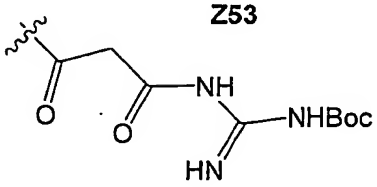

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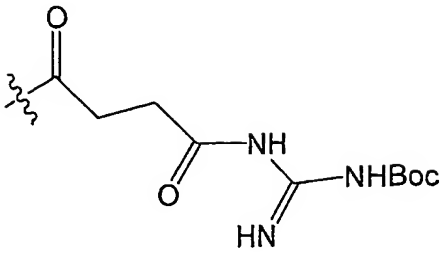

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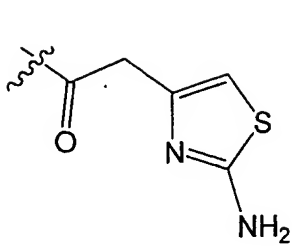

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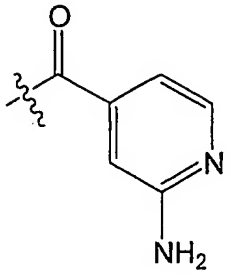

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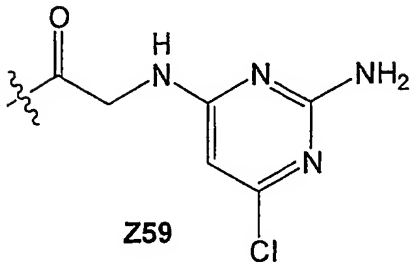

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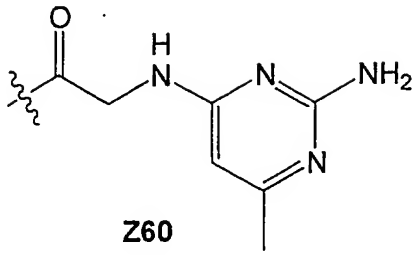
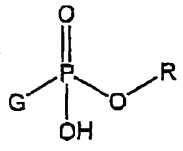
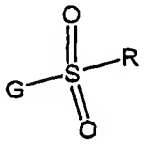
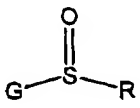
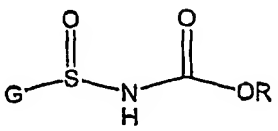
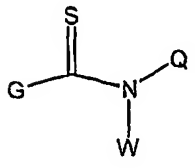
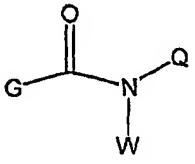
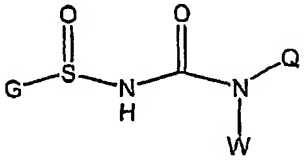
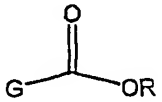
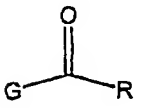
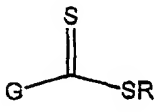
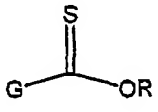
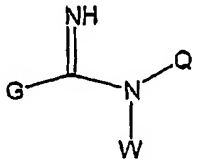


Z60

AMENDED CLAIMS

[received by the International Bureau on 07 November 2003 (07.11.03) ;
original claim 1 replaced by new claim 1 ;
remaining claims unchanged (1 page)]

and the groups Q and W are independently selected from hydrogen or R as is defined above, and Q and W may combine to form a cycle,

the groups Z and Y may combine to form a cycle,

the groups R1 to R5 may not combine together to form a cycle,

with the proviso that where two groups in the compound of formula I are N(Y)Z, these groups are different,

with the further proviso that when either R2 or R5 is N(Y)Z, N(Y)Z may not be trifluoroacetamido, acetamido, benzyloxycarbonylamino or t-butoxycarbonylamino,

with the further proviso that when R2 is N(Y)Z, N(Y)Z may not be phthalimido, 4-[*N*-[1-(4,4-dimethyl-2,6-dioxocyclo-hexylidene)-3-methylbutyl]-amino}benzyl ester (ODmab), *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde), 2,2,2-Trichloroethoxycarbonyl (Troc), 9-Fluorenylmethoxycarbonyl (Fmoc), or a 5-Acyl-1,3-dimethylbarbiturate type protecting group (DTPM),

with the further proviso that when the scaffold is of the 2-deoxy-2-aminoglucose configuration and R5 and R4 are both hydroxyl, R3 may not be a glycolate [-

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/01008

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07H 15/18, 5/06, 23/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Derwent Abstract Accession No. 2002-371191/40 Class B03 US 2002028927-A1 (CHRIST W. J.) 7 March 2002. See whole document.	1-5
X	US 6,184,366 B1 (CHRIST) 6 February 2001 See Claims and Examples; Columns 17-18	1-5, 6-21
X	WO 02/32915 A1 (ALCHEMIA PTY LTD) 25 April 2002 See whole document.	1-5

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2003	9 SEP 2003

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized officer

S.R. IDRUS
Telephone No : (02) 6283 2659

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/01008

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0099578 B1 (CIBA GEIGY AG) 1 February 1984 (& US 4,548,923 See column 6, formula III)	1-5
X	MALETIC M et. al., "Preparation of potential inhibitors of the mur-Pathway enzymes on solid support using an acetal linker", Bioorganic & Medicinal Chemistry Letters (2003), 13(6), 1125-1128. See page 1127 col. 2 Fig.2	1-5, 26
X	FUKASE Y et. al., "New efficient route for synthesis of lipid A by using affinity separation", Synlett (2001), (11), 1693-1698. See Scheme 1 compound 3, Scheme 3 compounds 17, 18, and 20	1-5
X	NAKAYAMA K et. al., "Novel peptidomimetics of the antifungal cyclic peptide Rhodopeptin: design of mimetics utilizing scaffolding methodology", Organic Letters. (2001), 3 (22), 3447-3450. See page 3448 Fig. 4 compounds 5 and 6	1-5
X	YOSHIZAKI H et. al., "First total synthesis of the Re-type lipopolysaccharide", Angewandte Chemie, International Edition (2001), 40(8), 1475-1480. See page 1477 col. 2 compounds 16 and 17	1-5
X	HANESSIAN S et. al., "Formation of 4-alkoxybenzylidene acetals on solid support and generation of functional diversity with carbohydrate scaffolds", Synlett (1999), (1), 102-104 See whole document.	1-5, 22-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/01008

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : **1-5 (in parts), 6-21**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-5 provide for such a vast number of possible compounds by virtue of the permutations of the variables present that they have not been fully searched. Claims 6-21 are directed to compounds of the invention as defined in Claims 1-5 wherein one or more of the hydroxyl oxygens are protected

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU03/01008

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	6184366	AU	63802/96	CA	2223140	CN	1192216
		EP	853627	HU	9802662	IL	122251
		JP	11506793	NO	975644	NZ	312299
		RU	2170738	ZA	9604666		
WO	02/32915	EP	1326873				
EP	0099578	AT	23536	AU	17218/83	CA	1243305
		CS	8305484	CS	8308406	DD	210058
		DK	3378/83	ES	524386	FI	832639
		GR	79611	IL	69292	JP	59033296
		NO	832691	NZ	205002	PL	243132
		PT	77081	SU	1299516	US	4548923
		ZA	8305357				

END OF ANNEX